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Original Communications

RETROLENTAL FIBROPLASIA

CLINICAL STATISTICS FROM THE PREMATURE CENTER OF THE CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

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RETROLENTAL fibroplasia, a lesion which occurs mainly in infants weighing 3½ pounds or less at birth, is manifested by a series of ocular changes leading gradually to a dense white vascular postlenticular opaque membrane.[1]

Increasing interest during the last eight years has led to reports from several centers indicating that the incidence of this distressing lesion varies roughly from 10 to 30 per cent in infants who weigh less than 1.5 kilograms (3 pounds, 5 ounces) at birth.[2, 3] In striking contrast to this frequency, very few cases have been encountered by personnel from the Departments of Pediatrics and Ophthalmology of Tulane and Louisiana State University Medical Schools. To verify this low incidence, and perhaps to determine what iatrogenic influences might be suspected, an attempt has been made to re-examine carefully all infants who weighed less than 1,500 grams at birth and who had been discharged from our premature nurseries during a two-year period ending Dec. 31, 1948. Although staff members of our two medical schools have seen such lesions originating in and around New Orleans, not a single example was recognized in any premature infants cared for in our premature center of the Charity Hospital of Louisiana during this period. Furthermore, we know of no premature baby who has developed this lesion among 3,752 who have been discharged from our premature nurseries during the past nine years. The daily census for premature infants in our hospital has grown steadily through the years, and now consists of about eighty-five babies receiving care on an average day.

Records of the infants in our study were carefully perused with a view of evaluating a number of factors that have been suspected as playing causative or contributory roles for an apparently increasing incidence of this lesion in other centers. Of the 131 infants discharged in this two-year period, and who weighed less than 1.5 kilograms at birth, it has been possible to secure satisfactory follow-up examination for this study in eighty

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TABLE I. BIRTH WEIGHTS OF 131 PREMATURE INFANTS

BIRTH WEIGHT (GRAMS)	INFANTS RE-EXAMINED	INFANTS REPORTED NORMAL; NOT EXAMINED	KNOWN DEATHS	NOT FOLLOWED
700- 799	1			
800- 899	2	1		1
900- 999	6		1	2
1,000-1,099	4	1		
1,100-1,199	12			3
1,200-1,299	10	1	1	3
1,300-1,399	20	3		6
1,400-1,499	25	10	6	12
Total	80	16	8	27

cases, and fairly adequate information as to the absence of any conspicuous ocular or visual abnormalities in an additional sixteen. Thus, ninety-six of the infants in this sample have been reasonably well accounted for. The characteristics of the group we were able to re-examine did not appear to differ from those of infants who could not be followed, so far as could be determined by a careful review of nursery records.

Of eighty infants for whom complete follow-up data were secured, all came from indigent families, and 65 per cent of the mothers came from New Orleans. Distribution by birth weight appears in Table I. It is known that eight of these 131 infants have subsequently died; four deaths were ascribed to broncho-pneumonia, one to hydrocephalus, one to an acute nutritional disturbance, and two to undetermined cause. Three died in our own hospital at 8, 6, and 5 months of age; no ocular abnormalities were described in any of them.

Careful funduscopic examinations after the pupils were well dilated were done for all eighty children who returned: since they were between 7 months and 2 years of age, early signs were not expected. No examples of retrolental fibroplasia were observed. Incidentally, we found four infants with concomitant internal squints, two with nonconcomitant squints, one with myelinated nerve fibers at the disc, one with a distinct arterial loop extending into the vitreous where the hyloid artery had been, and two with markedly elliptical discs. Another sixteen infants, not examined by us, were reported by their mothers to have satisfactory vision. If we assume, on the basis of other reports, that retrolental fibroplasia would be expected in at least 10 per cent of such infants, then the chances for encountering no cases in our sample would be three in one thousand.*[4] Furthermore the likelihood of missing a case of blindness would be remote, as parents of any baby with visual disturbance probably would have responded quickly to our request for information on this point.

Table II indicates the reported incidence of retrolental fibroplasia in several medical centers.[2] Most of these groups differed from ours in that preliminary inquiries concerning vision were sent to parents, after which only those infants with visual disturbances were examined by an ophthalmologist.

Data concerning weight and developmental progress were evaluated

*C. R. $= \frac{0-8}{\sqrt{80 \times .1 \times .9}} = 2.96,$
$P = .003$

TABLE II. INCIDENCE OF RETROLENTAL FIBROPLASIA

	WEIGHT GROUP (GRAMS)	WITH RLF	NORMAL	INCIDENCE RLF	% CASES FOLLOWED
New Orleans 1947-1948	1,500	0	80	0	61
Boston 1943-1947	< 1,361	10	28	26	97
	1,361-1,814	33	129	20	
Baltimore 1945-1947	< 1,361	4	29	12	?
	1,361-1,814	1	38	3	
Hartford 1948	< 1,361	4	3	57	100
	1,361-1,814	4	24	14	
Denver 1948	< 1,361	2	8	20	?
	1,361-1,814	0	4	0	

TABLE III. AGE AND PARITY OF MOTHERS OF 80 INFANTS EXAMINED FOR RETROLENTAL FIBROPLASIA

MOTHERS	AGE IN YEARS	MOTHERS	PARITY
10	15-19	21	0
28	20-24	20	i
16	25-29	14	ii
6	30-34	5	iii
8	35-39	3	iv
1	40-44	1	vi
11	Unknown	1	vii
		1	xi
		14	Unknown
80		80	

and considered to be similar to those of other infants who have been cared for in our unit before and since this study.

ANALYSIS OF THE DATA

In the following paragraphs are summarized data from the records of eighty infants which seemed even remotely pertinent to the etiology of retrolental fibroplasia; review of records for the remaining infants, who were not followed, failed to reveal any important difference from this larger group.

Sex and Color.—Thirty-three per cent of the babies were male, and 83 per cent of them were Negro.

Maternal Age and Parity.—Most of the mothers were less than 30 years old, and had had not more than two pregnancies (Table III). Sixteen of the eighty babies were twins, one was a triplet.

Complications of Pregnancy.—Four mothers had premature placental separations, two had pre-eclampsia, one had eclampsia, one had a genitourinary infection with sepsis, two had premature rupture of membranes (nine days and four days), one had chronic glomerulonephritis, and one had severe renal damage with terminal porphyruria.

Delivery.—Sixty infants were born in the hospital delivery rooms, forty-six spontaneously by vertex, seven by cesarean section, and seven by breech; twenty were delivered elsewhere.

Analgesia and Anesthesia.—Fifty-six mothers received no analgesia or anesthesia. Two deliveries followed sedation with Demerol and Amytal. Five sections were done under ether or inhalation anesthesia, one under local, one under spinal plus inhalation

anesthesia. Data as to medications for the remaining fifteen were incomplete.

Syphilis.—One mother was found to have syphilis and was treated with penicillin in the third month of pregnancy. At the age of 3 months, her infant was clinically well and had negative serologic tests for syphilis.

Neonatal Asphyxia.—Severe asphyxia occurred in three babies. For these artificial respiration by intratracheal catheterization was employed for periods of thirty, ten, and eight minutes according to the method of Russ,[5] before spontaneous respiration was initiated. In addition, equivocal evidences of asphyxia in more than one-half of the infants led to suctioning by intratracheal catheterization or bulb technique to maintain clear air passages.

Drugs Given to Infants in Delivery Units.—Caffeine-sodium benzoate was given to three infants, Metrazol to one, and Coramine to one; seventy-five babies received no drugs orally or parenterally.

Local Care of Eyes.—One per cent silver nitrate was instilled into all conjunctival sacs as required by health regulations. This was quickly irrigated with copious quantities of 0.9 per cent saline. Soon after arrival of the infants in the premature nursery, the eyes were again irrigated with boric acid and camphor drops.* Thirty-nine babies also received penicillin eye drops (1,000 U. per cubic centimeter distilled in water) four times every two hours during the first day. No other local care was given to the eyes. Aside from occasional transient conjunctivitis which we believed to be caused by such manipulations, no unpleasant side effects occurred.

Nursery Environment.—Our premature nurseries are completely air-conditioned and maintained at temperatures of 75° to 80° F. and relative humidity of 50 to 60 per cent. Sunlight may enter the rooms through large windows. Fluorescent ceiling lights are kept on night and day. No attempt is made to shield the infants' eyes.

Incubator Care.—Preheated incubators, warmed packs, and oxygen were available in delivery units for transfer of infants to nurseries. After admission, infants were usually kept in closed incubators* until a weight of about 1,800 grams was attained; at about this time, when temperatures were stabilized in open incubators, they were transferred to cribs.

Oxygen.—Oxygen† was used routinely at rates of four or more liters per minute to give concentrations approximating 50 per cent in the incubators for the first four weeks; longer if indicated by appearance or behavior of the baby.

Feedings and Neonatal Weight Loss.—Infants were fed with small soft rubber nipples on glass bottles; gavage was occasionally used. Feedings of water or 5 per cent glucose in saline were started at 12 hours of age; at 24 hours, formula was started and gradually increased to an intake of about 100 cal. per kilogram by the tenth day. Infants were fed one of three roughly isocaloric formulas; thirty-nine were given a mixture of evaporated milk and water with 5 per

*Boric acid gr. V, sodium borate gr. X, camphor water drams I.

*Gordon Armstrong, Model X-4.

†National Cylinder Gas Co.; purity 99.5 per cent.

TABLE IV. NEONATAL WEIGHT LOSS OF 80 PREMATURE INFANTS

AGE (DAYS) WHEN B. W. REGAINED	% OF CASES	% OF B. W. LOST	% OF CASES	DAY MINIMUM WEIGHT	% OF CASES
No Initial Loss	10	No Initial Loss	10	No Initial Loss	10
1- 5	7	1- 3	13	1- 3	17
6-10	28	4- 6	23	4- 6	39
11-15	13	7- 9	18	7- 9	15
16-20	16	10-12	14	10-12	5
21-25	12	13-15	10	13-15	7
26-30	8	16-18	6	16-27	7
31-35	3	19-26	6		
36-40	3				
	100%		100%		100%

cent carbohydrate,* twenty-nine one of one-half skim milk with Casec and 5 per cent carbohydrate,† and twelve one of condensed milk and water. No notable advantage of one type of formula over the other was noted. Data concerning neonatal weight loss appear in Table IV. Almost all infants had regained their birth weights before they were 1 month old, and more than half of them had done so before the age of 2 weeks. No infants lost more than 26 per cent of their birth weights and most of them lost less than 10 per cent.

Temperature Regulation.—Forty-three infants had daily variations in axillary temperature not exceeding 2° F.: thirty-seven infants had variations of more than 2° F., especially in the early period of adjustment. Temperatures were stabilized in the second week of life at levels below 97° F. in three infants, at 97° to 99° F. in fifty-five infants, and at or above 99° F. in twenty-two infants.

Oral Medication.—No infants received any high-potency multiple vitamin preparations. Vitamin C‡ was given in increasing amounts up to 100 mg. daily by the fourth day and continued in this dosage thereafter. Vitamin D* was started at 7 to 10 days, and gradually increased to intakes of 5,000 to 11,250 USP units daily by the age of 2 weeks. Sixty-one infants received iron and ammonium citrate in 10 per cent aqueous solution, calculated to furnish 15 mg. of elemental iron daily, beginning at 2 to 4 weeks of age. Nineteen received no supplemental iron.

Intravenous Medications.—Forty-one infants received one or more blood transfusions. Thirty-one infants received infusions of glucose, saline M/6 lactate, plasma or albumin. In addition, twenty-two were given fluids subcutaneously.

Intramuscular Injections.—On admission, all infants received a vitamin K precursor.† Twenty-five received 1 c.c. gamma globulin from human plasma and 1 c.c. vitamin D_3 in sesame oil.‡ Penicillin was given to thirty-three infants, sodium sulfadiazine to seven, and streptomycin to one.

Disorders Recognized During Hospital Course.—Twelve infants had

*Cartose.

†Made from Dryco and Cartose.

‡Cantaxin, Winthrop Chemical Co., synthetic crystalline ascorbic acid in propylene glycol, 2.5 mg. per drop.

*Drisdol, Winthrop Chemical Co., crystalline vitamin D_2 from ergosterol in propylene glycol, 250 U per drop.

†Hykinone, 2.4 mg., menadione sodium bisulfite per cubic centimeter, Abbott Laboratories, Inc.

‡Desynon, 100,000 units vitamin D_3 in 1 c.c. sesame oil, Winthrop-Stearns, Inc.

anemia considered to be of more than physiological degree, ten had diarrhea, three had proved sepsis, three had asphyxia at birth, three had superficial cutaneous abscesses, two had deep jaundice of undetermined etiology, two had thrush, and one had extensive atelectasis.

Hospital Stay.—Infants stayed in the nursery for an average of 76 days (41 to 142). Discharge weights averaged 2,665 grams (2,490 to 2,984 grams).

DISCUSSION AND CONCLUSIONS

Our study permitted no definite conclusion as to the cause of retrolental fibroplasia although several important differences in our plans of management of premature infants justify some speculation.

Among all factors considered which might conceivably be causative, no single one appeared to stand out. A recent report by Hepner and associates[6] casts suspicion on vehicles of certain high-potency, water-soluble, multiple vitamin preparations; the fact that no such preparations were used in our unit may add weight to their hypothesis. They have been used routinely at other centers where the incidence of retrolental fibroplasia is high. Our infants received no supplemental vitamin A; however, the Chicago group reports they were unable to relate the rise and fall of incidence to the institution of vitamin A therapy or its modification.

The suggestion has been made that excessive vitamin A and iron supplements may aggravate vitamin E deficiency which may, in turn, be important in causing retrolental fibroplasia.[7] Infants in our group received no supplemental vitamin E, but neither were their needs increased by excessive vitamin A or iron supplementation.

We could find no evidence to support inferences or suggestions that poor maternal nutritional status, light, silver nitrate used in conjunctival irrigation, or free use of penicillin or sulfadiazine were likely contributory factors. Likewise, the dosage, preparations, and combinations of vitamin C, D, and K, and iron used in our group were not thought to be contributing factors.

Anemia has been suggested as an etiological factor.[8] Our infants were transfused freely for minimal indications. Transfusions for hemoglobin levels below 10 grams per 100 c.c. were a routine practice.

Hypoprothrombinemia, leading to hemorrhage within the eye, has been considered as causal,[9] though there has been no real evidence in support of the point. All babies in our series received an intramuscular injection of 2.4 mg. of a vitamin K precursor as part of the admission routine.

Sublethal anoxia[10] was suggested as a cause of retrolental fibroplasia; it seems reasonable to believe that this factor would remain fairly constant in all parts of the country, even though its presence could not be established easily by ordinary means. Oxygen was liberally used for all the infants included in this study.

Deficient placental transfer of substances which might ordinarily be transferred through the placenta late in pregnancy has been proposed as an etiological factor.[9] This factor is difficult to evaluate but it could hardly be expected to vary around the country as the incidence of retrolental fibroplasia apparently has. None of

our babies were fed breast milk, and thus could not have received hormones or antibodies from this source.

There seems to be no reason to suspect climate or geographical factors as we have encountered several examples of retrolental fibroplasia from other hospitals in this area during this period.

Color is not likely an important factor. Though more than 80 per cent of our babies were Negro, the ratio of Negro to white premature infants at the Johns Hopkins Hospital was about 2:1 and the incidence of retrolental fibroplasia there was only slightly higher in white babies.[11]

We consider dehydration during the period of initial neonatal weight loss to be a possible contributory factor. In some centers where the incidence of retrolental fibroplasia is high, many prematures are given no oral feedings for two or three days,[12] whereas feedings were routinely started at 12 hours in our unit and efforts were usually made to minimize neonatal weight loss. The majority of our infants lost less than 10 per cent of birth weights; 58 per cent had regained birth weights within two weeks. We have seen no comparable figures as to weight loss for a group of prematures from areas where the incidence of retrolental fibroplasia is high. Excessive neonatal weight loss may be an important factor and deserving of further study.

SUMMARY

1. Eighty infants who weighed less than 1,500 grams (3 pounds, 5 ounces) at birth were examined after the age of 7 months for evidence of retrolental fibroplasia. The group included infants discharged from the Charity Hospital of Louisiana at New Orleans over a two-year period ending Dec. 31, 1948. No cases of retrolental fibroplasia were found.

2. An attempt was made to discover how the clinical management of these infants differed from that in areas with a high incidence of retrolental fibroplasia.

3. Although no single cause was found, suspicion as to the etiology of retrolental fibroplasia was directed at high-potency water-soluble multiple vitamin preparations or their vehicles, liberal iron supplementation, or excessive neonatal weight loss.

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LATER STATUS OF JUVENILE DIABETICS

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THE purpose of this study has been to determine the present status of the infants and children treated for diabetes mellitus at the St. Louis Children's Hospital during the first two decades of the insulin era. These patients all developed diabetes mellitus prior to 15 years of age and were cared for during childhood in a similar manner by the senior author (A.F.H.) and his staff. The principles of the method of their management have been previously published.[1] Following childhood, however, they have had care by a wide variety of methods. Not all maintained consistent and good control throughout life; in fact, twenty-two (or 44 per cent of those now over 15 years of age) spontaneously described a period of severe rebellion between 15 and 19 years of age during which time their concern for their diabetes was minimal and control poor. Because of such variations, it was thought worth while to attempt correlation of the duration of diabetes and the various factors which reflect control with the present physical status.

In the twenty-one-year period from 1922 to 1943, 180 juvenile diabetics have been treated at the St. Louis Children's Hospital. Sixty could not be located at this time; therefore, this report concerns only the remaining 120 cases. Of these, thirty would or could not cooperate, and thirty are known to be dead. When the mortality rate for the 120 cases is examined in approximately five-year periods, it is seen that an overwhelming majority of deaths, chiefly from acidosis, occurred in the first half of the study (Table I) and that deaths from acidosis did not occur in the later years (Table II).

In all, sixty patients returned for study, and the findings obtained from them form the main body of this report. The present age of the study group ranged from 10 to 40 years with a mean age of 22.5 years. The age of onset of diabetes varied from 6 months to 14 years with a mean age of onset of 6.1 years. There are twenty-eight females and thirty-two males. Distribution of the cases by duration is shown in Table III. Thus 69 per cent of the cases studied are of over ten years' duration and 31 per cent of ten years or less.

Each patient was interviewed by one of us for a careful analysis of his progress since last seen at the hospital, the history often being supplemented by progress notes in the hospital or outpatient records. He or she was then subjected to a careful physical examination; blood for serum nonprotein nitrogen determination was obtained, and written instructions were given for the collection of a urine specimen suitable for Addis count and determination of concentration ability by the Addis-Shevky method.

The *history* as obtained was then organized for evaluation into five parts on the basis of their apparent influ-

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

TABLE I. MORTALITY RATE OF 120 JUVENILE DIABETICS

DATE ONSET DIABETES	NO. PATIENTS	DEAD	PER CENT OF GROUP
1922 to 1928	33	12	36
1928 to 1933	23	14	69
1933 to 1938	20	4	20
1938 to 1943	44	0	
Total	120	30	25

TABLE II. CAUSES OF DEATH IN THIRTY JUVENILE DIABETICS*

CAUSE OF DEATH	DATE OF ONSET OF DIABETES				
	1922 - 1928	1928 - 1933	1933 - 1938	1939 - 1943	TOTAL
Acidosis	(6)	(5)	(1)	0	12
Pneumonia	1 (3)	1 (2)	(1)	0	8
Vascular disease	(1)	(2)	0	0	3
Pulmonary edema	0	0	1	0	1
Acute hepatitis	0	1	0	0	1
Peritonitis	0	(1)	0	0	1
Discontinued treatment	(1)	0	0	0	1
Unknown	0	(2)	(1)	0	3

*The figures shown in parentheses enumerate the patients whose deaths occurred elsewhere and in whom the details of terminal complications are unknown, or the patients who were brought to the hospital in a terminal condition and died before any response to therapy could be expected.

TABLE III. DURATION OF DIABETES

DURATION (YR.)	NO. CASES	PER CENT OF TOTAL
7 to 11	19	31
11 to 15	16	27
15 to 20	10	17
20 to 28	15	25

ence on the patient's diabetic state and on our ability to secure data relative to these factors.

Part 1. The patient's nutritional progress and present development were appraised with reference to his or her Wetzel Grid progress. A deviation of two physique channels was considered evidence of poor control (except as associated with pregnancy), and obesity was assumed if the patient had been in or above A_4 channel since the onset of diabetes.

Part 2. The incidence and severity of any intercurrent ketosis or acidosis since the onset of diabetes (initial ketosis and acidosis omitted). No patient was given points for absence of ketosis if he habitually omitted tests for ketonuria.

Part 3. The incidence and severity of clinically recognized hypoglycemic episodes. These seemed best evaluated in multiple rather than as individual episodes.

Part 4. The incidence of significant infectious or febrile illnesses as such. If acidosis, hypoglycemia, weight loss, or excessive glycosuria accompanied the illnesses, they were evaluated separately and included in Parts 1, 2, 3, and 5. Similarly, pregnancy was not considered here, but loss of control during a pregnancy was included in Parts 2, 3, and 5.

Part 5. The evaluation of degree of glycosuria in the absence of continuous records proved to be very difficult, and no completely satisfactory scheme was found to demonstrate the contribution of control of glycosuria to the patient's total control level. However, certain groupings emerged from the available data and seemed to indicate

the relative importance of this factor. In the process of preparing this report consideration was given to the complete omission of the factor of glycosuria in considering the patient's control, but this immediately resulted in an inability to differentiate control levels of patients whose clinical control and cooperation had been obviously different. The classification used is representative of the data obtained and in general is thought to reflect accurately the individual patient's interest and success in controlling glycosuria.

The following outline is the one used with the point values assigned. Each factor was considered equal and the patient awarded qualifying points, a perfect history of control resulting in a score of 100 per cent.

Criteria for the Evaluation of the Control Status

Nutrition

4—Not now obese and no period of obesity since onset.
4—No Wetzel Grid physique deviation exceeding two channels.
4—Not more than one episode of physique deviation exceeding two channels.
4—Not more than two episodes of physique deviation exceeding two channels.
4—Not more than three episodes of physique deviation exceeding two channels.

Acidosis

4—No period of ketosis since diabetic onset.
4—No clinical ketosis but no tests for ketonuria.
4—Not more than one episode of acidosis since diabetic onset.
4—Not more than two episodes of acidosis since diabetic onset.
4—Not more than three episodes of acidosis since diabetic onset.

Hypoglycemia

4—Mild hypoglycemic episodes not oftener than once or twice a month.
4—No hypoglycemia of a type such as usually requires hospital treatment.
4—Not more than one episode of hypoglycemia of severity that usually requires hospital treatment.
4—Not more than three episodes of hypoglycemia of a severity that usually requires hospital treatment.
4—Not more than six episodes of hypoglycemia of a severity that usually requires hospital treatment.

Infections

5—No severe intercurrent infection since onset of diabetes.
5—One severe intercurrent infection since onset of diabetes.
5—Two severe intercurrent infections since onset of diabetes.
5—Three severe intercurrent infections since onset of diabetes.

Glycosuria

5—Urine tests two or more times a day with average spill of 1 to 2 per cent and only rare single specimens showing 4 to 5 per cent sugar.
5—Urine tests daily in color range of blue to green with only occasional yellow or red specimens.
5—Urine tests every other day or weekly with estimated usual spill at 2 per cent. Occasional spill in excess of 2 per cent for periods not exceeding twenty-four hours.
5—Tests monthly or less, average spill thought to be light, no polyuria or polydipsia.

The physical examination was similarly separated into five main categories for the purpose of analysis and classification.

Part 1. The renal status as evidenced by the serum NPN, the Addis-Shevky concentration test, and the Addis count. The serum NPN was done by direct nesslerization of the Folin-Wu tungstic acid filtrate which in normal individuals gives a value below 40 mg. per 100 c.c. The urine specimens were collected as voided specimens; therefore, no effort was made to evaluate the white and epithelial cell counts. A 15 c.c. aliquot was concentrated thirty times by centrifuging at 1800 r.p.m. for five minutes; 14.5 c.c. of the supernatant were aspirated, and the sediment was resuspended in the remaining 0.5 c.c. The red blood cell count represents the average of all the squares counted in two standard chamber fillings (i.e., 1.8 c.mm.) under high power. The cast count represented the average of four standard chamber fillings counted under the low power (i.e., 3.6 c.mm.). These were then calculated for twenty-four-hour output. The red blood cell count was considered ele-

vated if it exceeded 1,000,000 cells per twenty-four hours, and the cast count was considered elevated if it exceeded 5,000 per twenty-four hours. The specific gravity was determined and corrected for protein and sugar content. A specific gravity of less than 1.026 was considered evidence of impairment of concentration ability.[2] In eight patients no urine specimen could be obtained; therefore, the total physical status grade was determined by interpolation. Five of these were in the 11- to 15-year duration group, one in the 15 to 20, and two in the 20- to 28-year duration group.

Part 2. The blood pressure was measured with a standard cuff and mercury manometer in the recumbent position; the degree of elevation was evaluated in relation to the normal blood pressure for the patient's age.

Part 3. The capillary fragility was determined by the method of Wright and Lilienfeld as described and modified by Donegan and Thomas.[3] A petechial count of ten was considered the upper limit of normal, ten to twenty-five petechiae denoting minimal, twenty-five to fifty moderate, and over fifty marked elevation.

Part 4. The retinae of each patient were examined under full mydriasis by an ophthalmologist and the findings classified as normal or as evidence of minimal, moderate, or advanced retinal disease. Grade I, or minimal retinal disease, was described as all those fundi which demonstrated not more than one to twenty microaneurysms or small round hemorrhages. These were thought to represent the earliest evidence of definite diabetic retinopathy. Grade II, or moderate retinal disease, was defined as all those with twenty or more microaneurysms or small round hemorrhages and/or large deep hemorrhages or superficial retinal hemorrhages (i.e., flame-shaped hemorrhages). Grade III, or advanced retinal disease, included any or all of the above plus evidence of arteriosclerosis, retinitis proliferans, vitreous hemorrhages, glaucoma, and rubeosis iridis. The eye findings have been made the subject of a separate report and are reported in greater detail elsewhere.[4]

Part 5. This part includes three unrelated but significant findings. These are enlargement to palpation of the liver, palpable evidence of sclerosis of the dorsalis pedis arteries, and evidence of trophic skin disease over the lower extremities.

The following outline is the one used to evaluate the various physical findings. In this section an attempt has been made to weigh certain findings in accordance with their importance and the apparent accuracy of the examining method in revealing vascular disease. Here again further experience may indicate readjustment of the values assigned.

Renal
5—NPN 40 mg. per cent or less.
5—No proteinuria.
5—Addis count abnormal in only one component (i.e., casts above 5,000 per twenty-four hours or red blood cells above 1,000,000 per twenty-four hours).
5—Addis count normal in both components.
5—Ability to concentrate to 1.026 or better (after correction for protein and sugar).

Blood Pressure
5—Normal blood pressure for age.
5—Not more than minimal elevation of the blood pressure for age.
5—Not more than moderate elevation of the blood pressure for age.

Capillary Fragility
5—Ten or fewer petechiae.
5—Twenty-five or fewer petechiae.
5—Fifty or fewer petechiae.

Eyes
10—Normal fundi.
10—Minimal fundus changes.
10—Moderate fundus changes.

TABLE IV. INCIDENCE OF VASCULAR COMPLICATIONS

COMPLICATION	NO. CASES	PER CENT OF TOTAL
Retinal disease	32	53
Increased capillary fragility	28	47
Renal abnormalities	17	32
Definite nephritis	8	15
Elevated blood pressure	13	22

TABLE V. INCIDENCE OF VASCULAR COMPLICATIONS BY DURATION GROUPS

	RETINITIS		INCR. CAP. FRAG.		NEPHRITIS		ELEVATED B.P.	
DURATION (YR.)	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
7 to 11	2	10	1	5	0	0	2	10
11 to 15	10	62	10	56	1	8	2	13
15 to 20	7	70	6	66	2	22	2	20
20 to 28	13	93	12	86	6	46	7	50

TABLE VI. MEAN CONTROL AND PHYSICAL GRADES, ALL PATIENTS

DURATION (YR.)	MEAN PHYSICAL GRADE	MEAN CONTROL GRADE
7 to 11	98	86.5
11 to 15	82	81.0
15 to 20	71	80.0
20 to 28	55	67.0

General
5—Liver not enlarged.
5—No palpable evidence of sclerosis of the dorsalis pedis arteries.
5—No degenerative skin changes over the lower extremities.

An over-all analysis of the incidence of vascular complications in the study group is shown in Table IV.

The single most significant factor in predicting the incidence of vascular complications appears to be the duration of the diabetes. In Table V the various complications are shown in duration group distribution and by per cent of cases studied in that duration group. It was also found that not only the incidence but also the severity of the complications increased as the duration of diabetes increased. This relation of the duration of diabetes to the incidence of vascular complications is well known and has been described in this series mainly to serve as an orientation to a study of the relation of level of control to the incidence and severity of vascular complications and, therefore, to the present physical status.

Before correlating the relation of control with physical grades, certain constants that influence each duration group must be considered. In Table VI there is demonstrated a progressive fall in the physical grade mean as the duration of diabetes increases. This is the expected change as the incidence of complications increases; however, in contrast, the control mean remains relatively constant until the twenty- to twenty-eight-year duration group is considered; then a sharp drop is noted. Two factors are offered in explanation of this unexpected drop. First, this duration group contains only a small number of well-controlled and a large percentage of poorly controlled patients. Second, this is the group exposed to the greatest number of control hazards (i.e., long duration, pregnancies, greater chronological age, and onset of their disease in the earliest days of insulin therapy). If again only those of under twenty years' duration are considered, the over-all control and physical grade averages might

suggest that control was of no significance and that progressive vascular degenerative disease continued regardless of the level of control. That this is not true will be demonstrated.

In addition, a certain incidence of vascular disease and nephritis may be expected in the nondiabetic population of similar age, but this incidence is too small to be used as a correction factor in this series.[5] As previously mentioned, attempt to give a numerical value to the level of control is difficult but necessary if the varied histories and physicals are to be compared. This problem is very real when the histories of those patients with clinically poor control are studied. In most of these, the control grade reached is probably higher than deserved but lack of interest and rare visits to a doctor make accurate evaluation of progress and indiscretions difficult. For the most part these patients tend to minimize their diabetes and consider poor care acceptable. In spite of the inaccuracies inherent in attempting to grade lack of control, when the physical grades of the patients with good and poor control are compared, a consistent difference is readily seen. This would suggest that the factors considered in arriving at a control evaluation do influence the incidence and severity of vascular complications.

The objective of the senior author's (A.F.H.) regimen for the management of juvenile diabetes has been the best possible control that can be obtained through education of the patient and his parents with a minimum of hospitalization and anticipation of normal growth, development, education, and play.

When the various factors in the criteria for control of this series are considered, the designation of an arbitrary control grade of 80 per cent as the dividing line between good and poor control appears logical. The development of grid status abnormalities should be completely avoidable. The patient who intelligently tests for ketonuria may be expected occasionally, with infections, to develop some ketosis, but this should not be allowed to go on to more serious ketosis and acidosis. Similarly, occasional mild hypoglycemic episodes may be expected with unusual work or play, but these should be aborted in their earliest stages by alert parents and patients. During the early years of regulation and education even the most conscientious, however, may mistakenly allow the development of a single serious episode of hypoglycemia before the premonitory signs and symptoms of hypoglycemia are well known to patient and parents. The incidence of serious infectious disease or febrile illness is not entirely under the patient's control, but with the advent of good antibiotic and chemotherapeutic measures, these can certainly be minimized. The patient's attention to the other factors in his regimen should also tend to minimize the incidence and severity of intercurrent infections. The adequate and intelligent control of glycosuria is within the means of all patients who are willing to avail themselves of the simple quantitative test kits available. In this series the patient's control of glycosuria seems to parallel his general interest and cooperation in control of his diabetes. Thus those patients whose control is considered poor by the criteria described show three times as many points lost under grid status as do those whose control is considered good. A difference of similar magni-

tude and direction is noted with regard to the criteria for acidosis, hypoglycemia, and glycosuria while those with poor control show five times as many serious infections as do their well-controlled companions. However, it must be recognized that even with a cooperative and intelligent family, over a long duration of diabetes, certain irregularities of control result which are probably not consistently and completely avoidable. Thus, a control grade of 80 per cent is what might be expected of a cooperative and intelligent patient under average conditions in childhood and as a young adult.

In arbitrarily selecting 80 per cent as the dividing point between those with good and poor control, it is recognized by us that an artificial difference is created between those with control grades of 79 and 80. However, when the distribution of values about the mean in each group is considered, it is found that relatively equal numbers of cases lie above and below the mean value and, therefore, would result in a relatively normal distribution curve.

The same duration groups utilized earlier in this report are again selected, and within each group those with good and poor control are contrasted as to their mean physical grade. Statistical analysis of the data was calculated by means of the "t" test as described by Snedecor[6] (Table VII). The differences obtained are highly significant except in the seven- to eleven-year duration group where no real difference was found. This latter finding is consistent with the prevalent opinion that evidence for the value of control is not seen in patients with diabetes of ten or less years' duration. If, however, the control level is important, the patients in the group should soon begin to show a higher incidence of complications than their more conscientious and cooperative companions. In contrast, the findings in the three groups of longer duration are striking and point clearly to the advisability of mak-

TABLE VII. RELATION OF PHYSICAL GRADE TO LEVEL OF CONTROL*

DURATION (YR.)	GOOD CONTROL			POOR CONTROL			T	P
	CASES	MEAN	S.D.	CASES	MEAN	S.D.		
7 to 11	13	98	3.2	6	97.5	4.2	0.28	.33
11 to 15	9	95	7.4	7	67.0	7.8	7.3	.002
15 to 20	4	94	9.4	6	57.0	14.0	4.4	.002
20 to 28	4	82.5	12.0	11	44.6	18.0	3.8	.003

*The statistical analysis of the data was calculated in each case and in the same manner throughout as follows:

1. The mean of the determinations under good and poor control was calculated and then the Standard Deviation of the Means by the formula:

$$x = \frac{S(x - \bar{x})^2}{n - 1}$$

2. The Standard Error of the Means was then calculated using the formula applicable to groups of unequal size:

$$S.E. = \pm \sqrt{\left(\frac{Sx_1^2 + Sx_2^2}{n_1 + n_2 - 2}\right)\left(\frac{n_1 + n_2}{n_1 n_2}\right)}$$

3. The significance of the difference between the two means was then determined by the "t" test according to the formula: $t = \frac{\bar{X}_1 - \bar{X}_2}{S.E.}$

4. The significance of the "t" value was then read from a "t" table and indicates the probability that the value for "t" would be exceeded by chance.

X = variate

$x = X - \bar{X}$ = deviations from mean

$\bar{X}$ = mean

S.D. = Standard Deviation

n = population mean

S = Sum of

TABLE VIII. INFLUENCE OF CONTROL ON RETINAL DISEASE

DURATION (YR.)	RETINAL GRADE						STATISTICAL ANALYSIS	
	GOOD CONTROL			POOR CONTROL				
	CASES	MEAN	S.D.	CASES	MEAN	S.D.	T	P
7 to 11	13	29.0	2.0	6	28.0	4.0	0.4	.33
11 to 15	9	26.7	5.0	7	14.3	5.3	4.7	.001
15 to 20	4	27.5	5.0	6	6.7	10.0	3.7	.006
20 to 28	4	22.5	5.0	11	7.3	10.0	2.8	.016

ing ever effort to maintain the best possible level of control in each patient.

In order to determine if the results were influenced by the age of onset of diabetes, present age, familial history of diabetes, or the daily insulin requirement, each of these factors was separately evaluated in the same manner, and in no case was there found to be a significant difference between the good and poor control groups. It is, therefore, assumed that any influence exerted by these factors would be equal on both groups and not a factor in the difference of mean physical grades observed within the duration groups.

If, now, the individual factors that contribute to the physical grade are studied in similar manner to determine the influence of good and poor control on the grade of the specific vascular complication, similar significant results are obtained.

All sixty of the patients in this series were submitted to careful retinal examination. This revealed fifteen cases (25 per cent) with minimal retinal disease, seven cases (12 per cent) with moderate retinal disease, and only ten cases (16 per cent) with advanced retinal disease. It is interesting to note that no patient with diabetes of less than fifteen years' duration had advanced retinal disease. The difference between the mean retinal grades of those with good and poor control and the statistical analysis of the difference is shown in Table VIII. These results parallel those found when the total physical grade was considered and would indicate that the careful examination of the fundus is an accurate method of detecting the early evidence of vascular complications and in the majority of cases closely correlates with the total physical profile.

The capillary fragility as performed by the previously mentioned positive pressure method was determined in fifty-nine cases. It was found to be within normal limits in thirty-one cases (53 per cent) and to show minimal elevation in nine cases (15 per cent), moderate elevation in twelve cases (20 per cent) and marked elevation in seven cases (12 per cent). The capillary fragility as an index of retinal disease was found to be misleading in only nine cases (15 per cent). When only those cases with increased capillary fragility and normal retinal findings are considered, only three such cases are found; thus 90 per cent of those with increased capillary fragility also had retinopathy. When the converse of this is examined, it is found that of those with retinopathy, 85 per cent also had increased capillary fragility. It would, therefore, appear that in this series while determination of the capillary fragility is a useful screening method, it is not as accurate an indicator of vascular disease as is careful retinal examination. Table IX shows the relation of the level of control to the

TABLE IX. RELATION OF CAPILLARY FRAGILITY TO CONTROL

DURATION (YR.)	GRADE CAPILLARY FRAGILITY						STATISTICAL ANALYSIS	
	GOOD CONTROL			POOR CONTROL				
	CASES	MEAN	S.D.	CASES	MEAN	S.D.	T	P
7 to 11	13	15.0	—	6	15.0	—	—	—
11 to 15	9	14.0	2.2	7	7.0	5.5	4.7	.001
15 to 20	4	11.0	4.8	5	7.0	5.7	1.1	.26
20 to 28	4	8.8	5.5	11	4.0	4.3	1.8	.09

mean capillary fragility grades. The difference in mean grade is noted in those over ten years' duration, but when the statistical significance of these differences is examined, they are found to be significant only in the eleven- to fifteen-year duration group in which group the difference is highly significant. Again no difference is noted in the seven- to eleven-year duration group where no cases of increased capillary fragility were found. The lack of significant difference in the fifteen- to twenty- and twenty- to twenty-eight-year duration groups may be explained by the higher average blood pressures observed in this group and the consequently higher midpoint between systolic and diastolic used for the test. Rodriguez and Root[7] in a similar study using a different method for the determination of capillary fragility conclude that increased capillary fragility occurs in diabetics as an early evidence of generalized arterial disease and is closely correlated with the development of retinitis and nephritis. It may be that the capillary fragility is an even earlier evidence of generalized vascular disease than we have found and that the lack of significant difference observed in those cases of long duration represents the factor of duration more accurately than control. This explanation would make more understandable the highly significant difference noted in the eleven- to fifteen-year duration group.

In the study of the patient's renal status, we have attempted by relatively simple and clinically available means to determine not only the presence of definite nephritis as manifested by albuminuria, increased urinary red blood cells, and increased urinary casts, but also to detect the incipient changes that in the apparently normal diabetic may herald the approach of clinical nephitis. By including the determination of the ability of the kidneys to concentrate and the blood nonprotein nitrogen determinations, we have attempted to differentiate those with early nephritis from those with severe impairment of renal function. Of the fifty-two patients from whom satisfactory specimens could be obtained, only nine patients (17 per cent) gave evidence of definite nephritis, and only three of these showed inability to concentrate or elevated blood nonprotein nitrogen. Elevation of the blood pressure was present in two-thirds of the cases classified as definite nephritis.

In Table X all abnormal renal findings have been considered in defining the individual renal grade, and the mean renal grades of those with good and poor control are compared and statistically analyzed. The blood pressure was determined in all sixty cases of this series and graded as minimally, moderately, or markedly elevated according to the patient's chronological age. No values obtained qualified for the latter classification; four cases (7

TABLE X. RELATION OF THE RENAL GRADE TO THE LEVEL OF CONTROL

DURATION (YR.)	GRADE OF RENAL STATUS						STATISTICAL ANALYSIS	
	GOOD CONTROL			POOR CONTROL				
	CASES	MEAN	S.D.	CASES	MEAN	S.D.	T	P
7 to 11	13	24.6	1.4	6	25.0	—	0.7	.33
11 to 15	7	25.0	—	4	17.5	6.4	3.3	.008
15 to 20	4	25.0	—	5	15.0	7.9	2.5	.04
20 to 28	3	23.0	5.3	10	12.5	2.9	2.3	.05

per cent) were moderately elevated, and nine cases (15 per cent) were classified as minimal elevation for age. With the exception of two cases of minimal elevation in the seven- to eleven-year duration group, all cases of elevated blood pressure were in the patients whose control has been classified as poor, but the incidence of elevated blood pressure was not as closely correlated with the other physical findings as was the incidence of retinopathy, increased capillary fragility, and abnormal urinary findings. Seven cases (54 per cent) of those with elevated blood pressure were in the twenty- to twenty-eight-year duration group. No study was made of the familial incidence of hypertension which may well be a factor in the results obtained.

SUMMARY

Follow-up data on 120 children who developed diabetes prior to 15 years of age has been presented. Thirty of these are dead, a gross mortality rate of 25 per cent, the majority having died from acidosis. Sixty were seen for a careful analysis of their progress and present physical condition, and the results thus obtained were organized for statistical evaluation. Those whose control level has been considered good are contrasted with those whose control level has been considered poor. The difference of physical grades of these patients who have had good and poor control is great enough to suggest that not only duration but also control is important to the incidence of complications in diabetes mellitus. While good control may not entirely prevent the onset of degenerative vascular disease, it may minimize its progress and, therefore, prolong the useful life of the individual. This in itself seems sufficient justification for the control of diabetes as carefully as is consistent with a relatively normal life for the individual. More experience and more well-controlled patients may demonstrate an even more important and specific role of control in the prevention of vascular complications of diabetes mellitus.

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A CLINICAL STUDY CONCERNING THE VALUE OF BIOLAC

III. Effect of Changes Introduced in New Improved Biolac Upon Growth of Young Infants

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THIS study was designed to discover whether certain changes in the constitution of a commonly used preparation for infant feeding, Biolac, would alter its previously demonstrated effectiveness[1] in producing satisfactory growth. Biolac, as introduced in 1937, contained milk fat 2.4 per cent, protein 2.8 per cent, carbohydrate (lactose) 8.2 per cent, and "available" iron 1.5 to 1.8 mg. per cent when reconstituted for feeding. The original study by Eley[1] indicated that the preparation was a satisfactory food for infants, and that its iron content was adequate for hematopoiesis. In 1943, Wolman and Borowsky[2] investigated the effects of various alterations in the original formula and concluded that an increase of fat content to 2.8 per cent and a decrease of lactose content to 7.4 per cent resulted in slightly fewer and somewhat more solid stools. These changes were therefore made and the preparation has been of that composition until 1948.

At that time it was felt that a further improvement might result from replacement of the original milk fat by a combination of destearinated beef fat and coconut oil, and lecithin, which release on saponification the higher fatty acids as shown in Table I. Since Jeans and Marriott[4] state that esters from cow's milk fat liberate somewhat more of the lower (more volatile) fatty acids, such as butyric and caproic, which are irritant, this substitution should tend to reduce even potential irritation to the gastrointestinal tract. Moreover, lecithin, as a source of choline[5] may afford further nutritional advantages. Because of the present trend toward vegetable rather than milk sugar in infant nutrition, about 60 per cent of the lactose was concurrently replaced by maltose-dextrin. The resultant preparation had the following composition as reconstituted for feeding, as compared to that manufactured between 1943 and 1948:

	*New Improved Biolac**	*Biolac*
Fat	2.8% (destearinated beef fat and coconut oil)	2.8% (milk fat)
Carbohydrate	7.4% (60% lactose, 40% maltose-dextrin)	7.4% (lactose)
Protein	2.8%	2.8%
Calcium	0.11%	0.11%
Phosphorus	0.8%	0.8%
Iron	0.0008%	0.0008%
Calories/ounce	20	20

In order to establish the rate of growth and the character of stools resulting from this new modification, a study was made of twenty-four matched pairs of infants during their first six months of age. One infant in each pair was fed the new preparation,

From the Department of Pediatrics, Harvard Medical School, and the Boston Lying-in Hospital.

Supported by a grant from the Borden Company.

*Official trade-mark name of new preparation.

TABLE I. THE COMPONENT FATTY ACIDS OF HUMAN MILK, COW'S MILK, AND BIOLAC FATS

FATTY ACID	PERCENTAGE WEIGHT		
	HUMAN[3]	COW[3]	BIOLAC
Saturated			
Butyric	0.4	3.0	0.1
Caproic	0.1	1.4	0.1
Caprylic	0.3	1.5	3.9
Capric	2.2	2.7	3.4
Lauric	5.5	3.7	23.0
Myristic	8.5	12.1	9.1
Palmitic	23.2	25.3	18.8
Stearic	6.9	9.2	10.1
Arachidic	1.1	1.3	0.1
Unsaturated			
Decenoic	0.1	0.3	Trace
Dodecenoic	0.1	0.4	Trace
Tetradecenoic	0.6	1.6	0.1
Hexadecenoic	3.0	4.0	0.1
Oleic	36.5	29.6	26.5
Octadecenoic	7.8	3.6	3.8
Lecithin: % of fat	1.70	0.85	1.93
% of milk	0.06	0.03	0.16

hereafter referred to as N.I.B., the other was fed equicaloric amounts of a standardized preparation of evaporated milk, corn syrup, and water, in the following basic proportions:

Evaporated milk (fortified with vitamin D)*	350 c.c.
Corn syrup	60 c.c.
Water	600 c.c.
Calories per ounce, approximately	20

Although the choice of this control feeding (hereafter designated E.M.M.) did not allow comparison with the earlier form of Biolac, it was selected as being a regimen commonly accepted as satisfactory for infants of mothers unable to provide human milk. A group of naturally fed infants would perhaps have been preferable as controls, but infants in whom one may confidently predict consumption of human milk for six months are not common in this area.

The criteria for matching test and control subjects, selected after discussion with a member of the Council on Foods and Nutrition of the American Medical Association, were similarity in:

(1) Race.

(2) Maternal parity, and age (within 5-year groups).

(3) General family history.

(4) Birth weight (within 250 grams), and birth length (within 3 cm.). No infants of less than 2,750 grams weight or 47 cm. length in either grou

Infants of non-nursing mothers were selected from the newborn nurseries of the Boston Lying-in Hospital in accordance with these requirements, and arrangements were made to provide them in the hospital with the test or control foods until discharge at the eighth or tenth day and at home thereafter until the end of the sixth month after birth. The preparation of food at home was done by the mothers. No cereal or vegetable was given to any infant before the fourth month, and thereafter the same cereal product*

*Borden's evaporated milk, vitamin D increased to 400 U. per reconstructed quart.

*Pablum, Mead Johnson & Co.

TABLE II. PHYSICAL GROWTH OF STUDY AND CONTROL INFANTS

	BIRTH		45 DAYS		90 DAYS		135 DAYS		180 DAYS	
	STUDY	(CONTROL)	STUDY	(CONTROL)	STUDY	(CONTROL)	STUDY	(CONTROL)	STUDY	(CONTROL)
Weight in Grams										
25th percentile	3,175	(3,048)	4,320	(4,139)	5,630	(5,315)	6,620	(6,237)	7,370	(6,910)
50th percentile	3,445	(3,345)	4,536	(4,394)	5,897	(5,740)	6,880	(6,804)	7,770	(7,519)
75th percentile	3,629	(3,657)	4,830	(4,819)	6,237	(6,265)	7,400	(7,434)	8,420	(8,440)
Length in Centimeters										
25th percentile	50.4	(50)	55.5	(54.0)	59.5	(58.9)	62.8	(62.6)	64.9	(65.5)
50th percentile	52	(51)	56.3	(55)	60.6	(59.8)	64.2	(63.8)	67	(66.6)
75th percentile	53.5	(52)	57.5	(56.6)	63	(62.3)	65.4	(65.2)	68.6	(68.5)
Head Circumference in Centimeters										
25th percentile			37.3	(37.25)	39.5	(39.25)	39.9	(40.65)	42.45	(42.35)
50th percentile			37.85	(38.15)	39.65	(40.2)	41.7	(41.65)	43.2	(43.45)
75th percentile			38.25	(38.65)	40.55	(41.2)	42.4	(42.4)	44.05	(44.35)

was provided for all, in roughly similar amounts. Small feedings of the usual fruits were allowed for all infants during the sixth month. Since both the N.I.B. and the E.M.M. contained supposedly adequate amounts of other vitamins except ascorbic acid, the only supplement furnished for all infants was a water-soluble ascorbic acid concentrate* in daily dosage of 50 mg. from 2 weeks of age.

Physical and Laboratory Measurements.—Physical examination was performed (in most instances by the same pediatrician) before discharge from the Lying-in Hospital, every two weeks until 3 months of age, and monthly thereafter. The usual body measurements were recorded. Hemoglobin concentration was measured photocolorimetrically once during the Lying-in Hospital stay and monthly thereafter; roentgenograph records of one upper and one lower extremity were made at the beginning and end of the study. Only one item of data, the daily frequency of stools, was necessarily left for maternal recording; this record was faithfully kept on a simple form by most mothers and turned in for transcription at each clinic visit.

*Cecon, Abbott Laboratories.

Results.—Although a few intercurrent infections and other minor disturbances occurred, the general health of all forty-eight infants remained comparable and satisfactory. In the N.I.B. group one infant had moderately severe pertussis at 18 weeks of age, a second had chicken pox at 19 weeks; bronchitis occurred in two infants, and otitis media in another. One of the E.M.M. infants also developed moderate pertussis just before the end of the study, a second had pneumonitis at 10 weeks, and another had recurrent respiratory infections.

Weight, length, and skull circumferences are set out in Table II. The most significant comparison in each category is that shown by the 50th percentile or median. It will be noted from Table I that, although the infants were matched in relatively narrow groups when selected, the N.I.B. subjects by chance were originally slightly heavier and slightly longer than were the controls. This difference in weight and length continued throughout the six months of observation. The median weights of the study group were further increased over their controls at the sixth month than was the case at birth, while the difference between median heights was

TABLE III. DISTRIBUTION OF HEMOGLOBIN CONCENTRATIONS IN STUDY AND CONTROL INFANTS

	(MEASUREMENTS IN GM./100 C.C.)					
	AGE: 4-8 WEEKS		11-15 WEEKS		24-28 WEEKS	
	STUDY	(CONTROL)	STUDY	(CONTROL)	STUDY	(CONTROL)
25th percentile	11.7	(12.0)	12.1	(11.15)	12.1	(12.0)
50th percentile	12.15	(12.5)	12.5	(12.15)	12.7	(12.45)
75th percentile	14.45	(14.55)	13.2	(13.15)	13.5	(13.3)

TABLE IV. ROENTGENOGRAPHIC FINDINGS AT 6 MONTHS OF AGE

	STUDY INFANTS		CONTROL INFANTS	
	BIRTH	6 MONTHS	BIRTH	6 MONTHS
Calcification of Long Bones				
Satisfactory films	22	23	22	21
Normal calcification	22	23	22	20
Subnormal calcification	—	—	—	1
*Ossification of Centers**				
Satisfactory films	21	23	19	22
Advanced	2	1	2	3
Average	19	21	16	19
Slow	—	1	1	—
Thickness of Subcutaneous Tissues†				
Satisfactory films	21	24	18	23
High	2	4	1	2
Moderate	16	16	14	17
Low	3	4	3	4

*Osseous development at birth considered advanced if seven or more centers visible, slow if three or less; at 6 months considered advanced if nine or more centers visible, slow if four or less.

†Subcutaneous fat at birth considered high if 11 mm. or more, low if 6 mm. or less; at 6 months considered high if 24 mm. or more, low if 16 mm. or less.

reduced. Neither of these trends is significant. The median (50th percentile) figure for skull circumference was insignificantly larger for the E. M.M. than for the N.I.B. infants throughout.

No infant presented any anemia. Although, as Table III indicates, the 50th percentile figures for hemoglobin concentration as measured between the fourth and eighth weeks showed a slightly higher level among the E. M.M. infants, the position at the end of the investigation had been reversed, the infants fed N.I.B. showing the higher level of hemoglobin concentration.

All roentgenograms were read by Dr. Harold Stuart, to whom much gratitude is hereby expressed. Three categories of progress were considered: (1) calcification of bone in general, (2) time of appearance of centers of ossification, and (3) thickness of subcutaneous tissue as a measure of nonskeletal growth.[6] Occasional films were not technically suitable for evaluating each of these factors. The results are briefly presented in Table IV. Calcification, considered normal in the films of all infants at birth, was read as subnormal at six months in only one infant. This was a member of the control group, whose subsequent course has been marked by the gradual appearance of mild chronic intestinal indigestion, although her stools were not abnormal during the six months of study. Osseous development and subcutaneous tissue thickness showed no significant differences between the two groups. No rickets or scurvy was discovered in either group.

Frequency of stools was greater among the younger than the older infants of both groups, as is brought out in Fig. 1. The chart, prepared from data recorded by the mothers, indicates that during the first 8 weeks after birth less than 30 per cent of all infants passed fewer than two movements daily. During this period, as shown in the first and second of the six diagrams in Fig. 1, the frequency of stools was somewhat greater among the infants receiving the N.I.B. After the eighth week, stool frequency was considerably reduced and the difference between the two groups of infants became negligible. Decline in frequency of stools appears at the same age in Wolman and Borowsky's earlier study.[2]

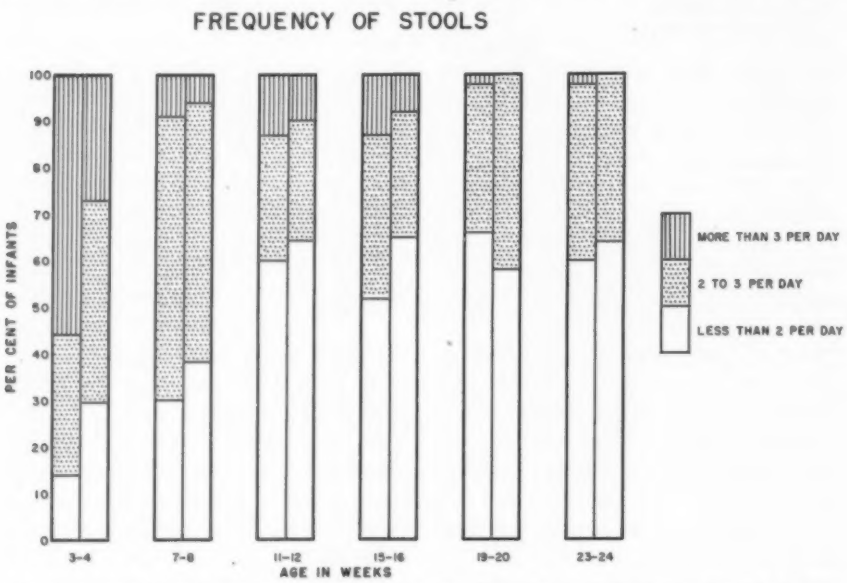

Fig. 1.—First column of each pair represents stool frequency in study group; second column, stool frequency in controls.

DISCUSSION

These findings may be considered from two aspects: first, the reliability of studies of this design, and second, the particular information secured by this one.

The critical evaluation of a food for normal infants poses the essential difficulty of avoiding or neutralizing other and variable factors which may also affect growth. This problem may be met either by using very large groups of subjects in order to smooth out the effects of nondietary variations, or by matching a relatively small number of test subjects with selected controls so that any combination of variable factors in the one is supposedly present to an equal degree in the other. The essentially similar character of growth in the two groups here presented, as shown by Tables II, III, and IV, suggests that the technique of matched pairs is an accurate method. Certainly it offers great advantages in efficiency.

Insofar as infection is concerned, the comparison between infants fed the New Improved Biolac and those fed a standard mixture of evaporated milk, corn syrup, and water showed no differences of any importance. Growth in weight, length, and head circumference, when compared at the 50th percentile or median level, were substantially similar. The differences in formation of hemoglobin, though slight, may reflect the high iron content of the experimental food, which is about ten times that of the evaporated milk mixture. While roentgenology of bones and soft tissues showed no significant differences between the two groups, the absence of rickets in all forty-eight infants indicates the sufficiency of vitamin D in either milk product used, at least for the first six months after birth. It is difficult to interpret the slightly greater frequency of stools in the group of infants fed N.I.B., unless as a chance effect or, more probably, as related to some other dietary factor than the fatty acid intake. The difference in stool frequency was, however, not of large degree and during most of the age period studied was a negligible one.

SUMMARY AND CONCLUSIONS

The composition of a commonly used infant food, Biolac, has been altered by the substitution of coconut oil and destearinated beef fat for the milk fat originally used, and by replacement of about 60 per cent of the lactose content by a maltose-dextrin combination. To determine the effectiveness of this preparation, twenty-four matched pairs of infants were studied through the first six months of life. One infant of each pair received the new food, the other received a conventional evaporated milk, corn syrup, and water formula.

Physical, roentgenological, and hematological measurements indicated satisfactory and quite similar courses for both groups of infants, with slightly greater hemoglobin concentration being attained by the study as compared to the control infants.

Infections occurred with similar low frequency in both groups of infants. Stool frequency was slightly greater among the infants of the test group. Since their food included less of the volatile fatty acids of cow's milk, this suggests that the cause of this difference was not related to a fatty acid factor.

It is concluded that the matched pair technique offers a reliable method of utilizing relatively small groups of infants for growth studies of this type. By that technique the preparation now marketed as New Improved Biolac appears to be an entirely satisfactory food for promoting proper growth in young infants.

The assistance of Miss Elizabeth Quinn and Mrs. Clinton E. Piper is gratefully acknowledged.

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METHYLENE BLUE IN THE TREATMENT OF METHEMOGLOBINEMIA IN PREMATURE INFANTS CAUSED BY MARKING INK

A Report of Eight Cases

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THE following cases of methemoglobinemia resulting from the use of aniline-containing ink in the marking of diapers are reported to emphasize the dangers of such procedures and to demonstrate the rapid cure following the use of methylene blue.

Methemoglobinemia due to various causes is not uncommon. Drabkin[1] has ascertained the methemoglobin content of the normal erythrocyte to be 0.5 per cent or less of the total pigment and has observed that a minimum of 1.5 Gm. per cent must be present in the peripheral blood for visible cyanosis to be present. Abnormalities in cellular reduction of methemoglobin are thought to play a part in the etiology of congenital and idiopathic methemoglobinemia of which there are several cases reported in the literature.[2-10] These patients have been treated with ascorbic acid and/or methylene blue. The role of triosephosphate and lactate and of coenzymes I and II in the reduction of methemoglobin in the red blood cells has been pointed out by Gibson[8] and Drabkin.[1] Gutmann, Jandorf, and Bodansky[9] feel that the essential feature in the reduction of methemoglobin within the intact erythrocyte or in solution is the interaction between diphosphopyridine nucleotide and methemoglobin. They have postulated that diphosphopyridine nucleotide reduces methylene blue to leucomethylene blue which in turn reduces methemoglobin to hemoglobin. Wendel[11] in 1939 demonstrated that methylene blue can cause both the formation and disappearance of methemoglobin from the blood stream and along with Hartmann, Barnett, and Perley[12] was among the first to demonstrate the use of this agent in the treatment and prevention of methemoglobinemia.

Efforts to explain the so-called "idiopathic" hemoglobinemia have been made by Cornblath and Hartmann.[13] Their observations explain the role of bacteria and pH of the upper gastrointestinal tract of infants in the reduction of nitrates, which may occur in drinking water, to nitrites, the nitrites so formed being capable of producing methemoglobin with cyanosis. Many instances of "idiopathic" methemoglobinemia are in reality to be attributed to the ingestion of water containing nitrates. Numerous reports from various sections of the country have shown that drinking of nitrate-containing well water and the ingestion of bismuth subnitrate is responsible for cyanosis due to methemoglobinemia in infancy.[14-30] These reports include the use of methylene blue and ascorbic acid in the treatment of this con-

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dition. However, the observations of Cornblath and Hartmann,[13] Dowell,[21] Finch,[31] Walliker and Baxter[32] in human beings, and Bodansky and Gutmann[33] in cats conclude that methylene blue is more rapid in its action and is the drug of choice.

During the past five years there have been several reported episodes of methemoglobinemia in premature and full-term infants resulting from the use of diapers stamped with aniline-containing ink.[34, 35, 36] Also the ingestion of wax crayons which contain aniline derivative have been the cause of methemoglobinemia in older children.[37, 38, 39] Other medicinal agents such as acetanilid, acetophenetidin, Plasmochin, sulfanilamide, and Promin should be mentioned because of their known property of producing methemoglobin.

SUMMARY OF CASES

On Dec. 5, 1949, a call was received from the premature nursery that several of the premature infants had rather suddenly become listless, refused to take their formulas, and appeared to be dusky in color. Upon entering the nursery it immediately became obvious that the atmosphere contained an appreciable quantity of free aniline. As the incubators were approached and opened, the odor of aniline was intense, and the infants were observed to be in a state described above. The diapers were promptly examined and observed to be new and freshly stamped with an ink containing aniline; letters ranging in size from one to one and one-half inches as follows:

"John Gaston Hospital
N. B. N."

The marking department on two previous occasions had been urged to take precautions against the use of such ink.

The age, weight, birth weight, sex, and race are summarized in Table I, and the total hemoglobin, per cent methemoglobin, total methemoglobin, degree of cyanosis, and quantity of methylene blue administered are summarized in Table II.

Seven of the eight infants had visible cyanosis of the mucous membranes and nail beds; being Negro infants the cyanosis of the skin was not equally conspicious in all cases. The cardiac findings were not remarkable, and the respiratory rates were not unusually rapid. Listlessness and central nervous system depression were obvious.

Blood specimens were taken from the femoral vein and examined spectrometrically for methemoglobin content. Total hemoglobin was determined colorimetrically

Promptly after obtaining the above blood specimens each infant was given 1.5 mg. per kilogram of methylene blue as a 0.1 per cent solution via the scalp vein. Within twenty minutes after injection and before the eighth infant had received its methylene blue, the first infant was definitely losing the cyanosis. Thirty minutes after completion of the injection in the eighth infant, all infants were non-cyanotic, and the peripheral blood had changed from the deep chocolate brown color, initially observed, to a bright red color. The course from this point was uneventful and all infants continued to make a continuous weight gain not unlike that observed prior to the poisoning.

TABLE I. SUMMARIZING DATA

NAME	BIRTH DATE	BIRTH WEIGHT (GRAMS)	AGE (DAYS)	WEIGHT (GRAMS)	RACE	SEX
M. D.	11/29/49	1,503	6	1,616	Negro	F
J. R.	11/25/49	1,588	10	1,785	Negro	F
L. R.	11/25/49	1,613	10	1,843	Negro	F
B. S.	11/ 9/49	1,985	26	2,386	Negro	M
J. H.	11/18/49	1,106	17	1,361	Negro	F
C. Q.	11/25/49	1,503	10	1,644	Negro	F
B. H.	11/11/49	1,332	24	1,644	Negro	F
P. S.	11/11/49	1,418	24	1,758	Negro	F

TABLE II. CHEMICAL DATA, DOSAGE OF METHYLENE BLUE, DEGREE OF CYANOSIS

NAME	INTRAVENOUS METHYLENE BLUE (MG./KG.)	HEMOGLOBIN (GM./100 C.C.)	METHEMOGLOBIN (% HG)	METHEMOGLOBIN (GM./100 C.C.)	CYANOSIS
M. D.	1.5	10.5	30	3.15	4+
J. R.	1.5	10.0	50	5.0	4+
L. R.	1.5	9.5	40	3.8	4+
D. S.	1.5	12.0	10	1.2	?
J. H.	1.5	9.5	60	5.7	4+
C. Q.	1.5	11.0	50	5.5	4+
B. H.	1.5	9.5	40	3.9	4+
P. S.	1.5	11.0	55	5.5	4+

DISCUSSION

From Table II it is obvious that severe methemoglobinemia was caused by the aniline-containing dye in seven out of eight cases in this group of premature infants. Because of the apparent high concentration of aniline in the atmosphere, it is quite likely that the absorption of the aniline was by way of the respiratory tract as well as the skin. The severe methemoglobinemia, along with an existing slight weight, imposed a handicap which might have terminated tragically; nevertheless, methylene blue in a dose of 1.5 mg. per kilogram caused a rapid recovery and in no instance did the usual course of prematurity appear to be altered. This observation confirms those of Cornblath and Hartmann, Dowell, Finch, Walliker, and others to which previous references have been made, i.e., that methylene blue is rapid in its action. It is because of this conception that ascorbic acid was not used in any of these premature infants; if the toxicity had occurred in full-term infants both agents would have been used in alternate cases for comparison.

SUMMARY

Eight cases of methemoglobinemia resulting from the use of aniline-containing ink to mark diapers are reported. Prompt relief and complete recovery followed treatment with intravenous methylene blue in each case.

A brief review of the literature is included.

The assistance of Dr. E. F. Williams, Associate Professor of Chemistry, with the blood analyses for methemoglobin is acknowledged.

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THE RELATIONSHIP BETWEEN INFANT FEEDING EXPERIENCE AND LATER BEHAVIOR

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IT HAS been frequently noted that a relationship between early infant feeding experience and later behavior exists. Such acute observers of the human scene as Aldrich and Aldrich,[1] Frank,[2] Fenichel,[3] Anna Freud,[4] Maloney,[5] Ribble,[6] and Spock[7] have noted its existence. Research workers such as Childers and Hamil,[8] Escolona,[9] Hoefer and Hardy,[10] Holway,[11] Levy,[12] Maslow and Szilagyi-Kessler,[13] Pearson,[14] Roberts,[15] Rogerson and Rogerson,[16] and Trainham[9] have also found a relationship between early infant feeding experience and later behavior.

This relationship between early feeding and later behavior is often interpreted as an indication of cause and effect. It is implied by some of the writers that the likely reason for the relationship is the fact that feeding experience leaves some mark on the infant which influences its later behavior. Other writers, including Orlansky,[17] feel that a cause and effect relationship should not be assumed and emphasize the importance of other related factors.

The purpose of this paper is not only to explore the relationship between infant feeding experience and later behavior but also to explore its possible causes.

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METHODS

Twenty-four normal children were studied intensively for indications of many possible trends. They were a tuition-paying group of twelve girls and twelve boys whose ages ranged from 5 years, 3 months to 6 years, no months.

The feeding information was obtained in a private interview with each mother. The mothers were asked to say how they fed their children, and the information was written down in the order the mother related it. The exact wording of the questions varied from interview to interview. Most questions were simple and direct. However, practice interviews had revealed that the subject of breast feeding and whether the bottle was held were best approached in an oblique manner as mothers tended to be easily antagonized by direct questions on these subjects. Every effort was made to encourage the mother to talk spontaneously without the help of questions, and nineteen (79 per cent) of the mothers volunteered pertinent background material as well as giving the minimum solicited information.

There were two checks on the accuracy of the material given in the interview. Each parent filled out a fifteen-page questionnaire* for the

*The questionnaire was compiled by the principal of the school, George E. Raab, Ed.D., in cooperation with his teachers. It covered many aspects of the child's development, environment, and personality.

TABLE I. AGREEMENTS BETWEEN FEEDING INFORMATION FROM DIFFERENT SOURCES

	NUMBER OF COMPARABLE ANSWERS	PER CENT OF COMPARABLE ANSWERS THAT AGREED
Parents' Questionnaire vs. Interview Data		
Duration of breast feeding*	24	92
Difficulty in finding satisfactory formula	24	96
Date of giving up last bottle	24	92
Schedule rigidity†	7	100
Doctor's Questionnaire vs. Interview Data‡		
Duration of partial breast feeding*	6	83
Duration of complete breast feeding*	6	100
Early schedule	7	86
Maternal attitude toward baby	5	80
Appetite in infancy	7	100
Difficulty finding satisfactory formula	7	71

*Since weaning from the breast often takes several weeks, only a discrepancy of more than a month was counted as a disagreement.

†Due to the generality of the question on schedules in the questionnaire, answers were comparable only in those cases where added specific explanations were written in by the parent.

‡Most doctors felt unable to answer all the questions in their questionnaire. So few felt they knew the answers to whether the child was fed half hour early, and age when the last bottle was given up, that these have been omitted from the tabulations.

school which contained several items of information comparable with the interview material. Pediatricians' reports were also available in seven (29 per cent) of the cases. Table I summarizes the agreements between interview material and material from other sources on several items of information. Although it was impossible to check the accuracy of the other items, the close agreement on the checked items shows that the mothers were cooperative, and capable of remembering details about feeding their infants.

Information on the children's behavior and environmental background came from both parents and the kindergarten director. The parents gave the material during the interview and in the extensive school questionnaire. The school reports of the kindergarten director were used. She also filled out a behavior rating scale which was especially constructed to cover fifty-two aspects of the child's behavior which could be observed in this kindergarten. The rater was required to check the phrase or sentence which best described the behavior of the child.*

RESULTS

The feeding information was studied to discover what patterns of feeding experience existed in the group. Table II gives the definitions and details of the patterns found.

The relationship between early feeding and later behavior is summarized in Table III. The following trends can be seen in this table:

Breast Feeding Groups Compared.—The abortive and successful groups showed the most desirable behavior. They had the highest average adjustment scores, were the most popular with children, showed the most friendliness toward both children and adults, and took the most

*The adequacy of the behavior rating scale for gathering a mass of descriptive material about the child's behavior was checked as follows: A student teacher rated five children independently of the kindergarten director, making a total of 236 comparable judgments. Fifty-three per cent were in complete agreement; 45 per cent showed differences in degree in the adjective chosen; and only 2 per cent were contradictory. This low rate of contradiction can be partly accounted for by the fact that no judgments were forced as it was possible to check "don't know" on every item. Keeping the judgments on the behavior level eliminates the subjective step of interpreting behavior in terms of personality traits.

TABLE II. THE FEEDING PATTERN GROUPS*

GROUP	DEFINITION	NO. IN GROUP	VARIATIONS WITHIN GROUPS
Breast Feeding			
Never	Never put to the breast	6	Score†: 0
Abortive	Brief attempts to breast feed	8	Mean 2.5 Score†: Range 1 to 5
Supplemented	Prolonged periods of breast feeding requiring bottle supplementation most of the time	6	Mean 14 Score†: Range 9 to 20
Successful	Prolonged periods of breast feeding without bottle supplementation	3	Mean 46 Score†: Range 36 to 58
Schedules			
Rigid	Schedule adhered to so strictly that if the baby seemed hungry a half hour early he was not fed	11	4-hour schedule; child occasionally fed 5 to 10 minutes early
Less rigid	Although definite limits to the flexibility of the schedule existed, the baby was fed a half hour early if he seemed hungry	6	3 cases—half hour was near limit of flexibility; 3 cases—distinct effort to keep to feeding plan
Flexible	Feeding times were completely variable	5	2 cases fed on demand; 3 cases flexible through the day and no schedule at night
Weaning Experiences			
Early	The last bottle was given up during the first year	10	8 months to 1 year
Late	The last bottle was given up after the first year	14	8 cases under 2 years; 6 cases 2 years and over
Unheld	Bottle holding was omitted so young that bottle propping was necessary	3	Bottle propping started 0 to 4 months
Sudden	Sudden withdrawal of accustomed mode of feeding	4	1 case—sudden withdrawal from breast offering bottle substitute; 3 cases—sudden withdrawal of bottle offering cup substitute
Feeding Reactions			
Feeding resistance	Attempts to force more food intake	5	Persistent attempts to get the formula into the baby
Formula reactions	Continued difficulty in finding satisfactory formula	5	At least a month of formula troubles; two so severe that all milk was stopped
Weaning reactions	Reactions to the weaning from the bottle	6	Intensity varied from crying every night for months and refusing cup milk ever since to refusing milk temporarily but accepting chocolate milk immediately
Other reactions	Reactions centered about the feeding situation but not around weaning	7	2 cases of trouble about dropping 2 A.M. feeding. 2 cases of continuous screaming coupled with avid appetite. 1 case of hating breast. 2 cases of vomiting or hating solid food

TABLE II—CONT'D

GROUP	DEFINITION	NO. IN GROUP	VARIATIONS WITHIN GROUP
Mixed Experiences			
Less rigid—supplemented	Supplemented breast feeding on a less rigid schedule	3	
No trauma	No experience with unheld bottles, sudden weaning, feeding resistance, formula reactions, weaning reactions, or other reactions	7	

*Due to sudden change in patterns or insufficiency of detail, one child has been omitted from breast feeding tabulations and two from all schedule tabulations in this and all subsequent tables.

†Score was calculated by giving one point for each week of partial breast feeding and two points for each week of complete breast feeding.

responsibility. In addition to this, the abortive group most frequently fed themselves by 18 months of age and had a high average social adaptability score, while the successful group all preferred to play with older children. The supplemented group had the lowest average adjustment and average social adaptability scores, daydreamed the most, and were seldom chosen as playmates. The never group disturbed other children at work and play more than the other breast feeding groups. Both the never group and the supplemented group liked to show off and act silly.

Schedule Groups Compared.—In general, the flexible group showed the most desirable behavior and the less rigid group showed the least desirable behavior while the rigid group fell in between the two. The flexible group had the highest average adjustment and average social adaptability score, and were most popular with other children, least self-conscious with adults, and the least likely to show off and act silly. None of them were frequently led by other children, and none preferred to play with older children. The less rigid group were the least friendly toward other children, and were seldom chosen as playmates. They were the most resistant to adult suggestions, the most self-conscious with adults, needed the most reminding to do routine things, and were less likely to take responsibility well. The rigid group led other children by giving commands more frequently than the other schedule groups and were less shy and more friendly toward adults. The rigid group was mediocre containing none of the best or worst adjusted children in the total group.

Weaning Groups.—Although the average adjustment scores and average social adaptability scores of the early and late weaned groups were about the same, a larger proportion of the early weaned group was friendly toward adults and children, accepted adult suggestions, took responsibility well, and led frequently by giving commands. The late weaned group daydreamed more, and contained all the best and worst adjusted children in the total group.

The sudden group did not differ markedly from the total group, but the unheld group did. They had low average adjustment and social adaptability scores. They did not accept

TABLE III. BEHAVIOR OF THE

GROUPS	NUMBERS IN GROUPS	AVERAGE ADJUSTMENT SCORE (2)	ADJUSTMENT SCORE RANGE	AVERAGE SOCIAL ADAPTABILITY SCORE (3)	ESPECIALLY SOUGHT AFTER AS PLAYMATE (%) (4)	SELDOM CHOSEN AS PLAYMATE (%) (4)	FRIENDLY TOWARD OTHER CHILDREN (%) (4)	DISTURBS OTHERS AT WORK OR PLAY (%) (4)	FREQUENTLY LEADS BY GIVING COMMANDS (%) (4)	FREQUENTLY LED BY OTHER CHILDREN (%) (4)	PREFERS TO PLAY WITH OLDER CHILDREN (%) (5)
	GENERAL TRAITS				BEHAVIOR WITH CHILDREN						
Breast Feeding											
Never	6	- 7	-20 to +20	1.5	17	0	50	83	33	17	50
Abortive	8	+ 3	-20 to +30	2.1	63	0	88	13	50	13	25
Supplemented	6	-20	-40 to 0	0.7	33	50	33	33	33	33	17
Successful	3	+10	-10 to +40	1.3	67	0	100	33	33	33	100
Schedules											
Rigid	11	- 7	-20 to +10	1.5	45	0	73	27	64	36	45
Less rigid	6	-13	-40 to +40	0.7	33	50	33	50	17	33	50
Flexible	5	+ 2	-20 to +20	2.0	80	0	80	40	20	0	0
Weaning											
Early	10	- 3	-20 to +20	1.6	60	10	80	30	70	20	50
Late	14	- 7	-40 to +40	1.4	36	14	50	43	14	29	29
Unheld	3	-17	-20 to -10	0.3	33	33	33	67	0	33	67
Sudden	4	-10	-20 to 0	1.3	25	0	75	25	25	50	50
Reactions											
Feeding resistance	5	- 6	-20 to +10	1.6	20	0	60	40	60	20	100
Formula reactions	5	- 6	-20 to +10	1.6	60	0	60	40	40	40	20
Weaning reactions	6	- 8	-40 to +40	1.5	50	17	50	50	33	17	50
Other reactions	7	-10	-40 to +10	1.3	43	14	57	43	43	29	43
Mixed Experiences											
Less rigid-supplemented	3	-30	-40 to -20	0	0	100	0	67	0	33	33
No trauma	7	0	-30 to +30	1.9	57	14	57	29	29	14	0
Total Group	24	- 5	-40 to +40	1.5	46	13	63	38	38	25	38

(1) Of the seventy-two traits of behavior studied in all, only those showing especially suggestive trends are included in this table. Due to the large number of behavior items studied on such a small group, some decided trends would occur by chance.

(2) *Adjustment Score* is a measure of adjustment varying from +40 for the highest possible adjustment to −40 for the lowest adjustment. Good adjustment was defined as coping adequately with problems of everyday living. The score was calculated as follows:

The behavior material on each child from all sources was organized into behavior profile sheets. Each child had four profile sheets covering: (1) behavior with adults; (2) behavior with children; (3) habits connected with food, sleep, elimination, nervousness, etc.; (4) other personality characteristics. These behavior profile sheets were submitted to two judges—one who was inclined to judge behavior in terms of Gesell norms and the other who tended to interpret behavior in psychoanalytic terms. Each judge sorted the profiles into a better and a less well-adjusted group. Each profile was considered −10 if both judges found it less well adjusted and +10 if both found it better adjusted, and zero if the judges disagreed. The profile scores for each child were added together and thus their adjustment score could vary between +40 and −40. The validity of these adjustment scores is indicated by the fact that the one child

FEEDING PATTERN GROUPS (1)

BEHAVIOR WITH ADULTS						PERSONAL HABITS						
FRIENDLY TOWARD ADULTS (%) (4)	ACCEPTS ADULT SUGGESTIONS (%) (4)	SELF-FEEDING AT 18 MONTHS (%) (5)	CHANGES BEHAVIOR AS ADULT APPROACHES (%) (4)	NEVER SELF-CONSCIOUS WITH ADULTS (%) (4)	OFTEN NEEDS REMINDING TO DO ROUTINE THINGS (%) (4)	TAKES RESPONSIBILITY WELL (%) (4)	NEVER LIKES TO SHOW OFF OR ACT SILLY (%) (4)	SHY (%) (5)	DAYDREAMS (%) (4)	ENURESIS (%) (5)	INDIFFERENT APPETITE IN CHILDHOOD (%) (6) (7)	SUCKING HABITS PERSISTING INTO FIFTH YEAR (%) (6)
50	67	17	67	17	0	33	33	33	50	0	80	50
88	75	50	38	50	0	88	63	25	38	13	57	25
67	50	0	50	33	33	17	17	50	83	33	75	50
100	67	0	0	33	33	67	67	0	33	0	50	33
91	91	27	36	36	0	64	36	18	55	9	50	55
50	17	0	50	17	50	17	50	50	67	33	80	33
60	80	40	40	60	0	80	80	60	60	0	50	20
90	90	30	30	40	10	70	50	20	40	20	56	30
57	43	14	50	29	14	36	43	43	71	7	80	43
100	0	0	67	33	67	0	0	0	33	33	0	100
75	50	0	0	0	0	25	25	50	75	0	75	25
100	80	40	40	60	0	40	40	0	20	20	80	20
80	80	0	40	40	0	80	0	20	80	20	50	80
67	33	0	33	17	33	17	33	50	67	17	100	33
86	71	14	43	43	14	57	14	14	57	29	80	29
33	0	0	100	0	67	0	33	67	100	67	67	33
43	57	43	57	43	0	57	86	57	57	0	80	14
71	63	21	42	33	13	50	46	33	58	13	68	38

the kindergarten director considered to be a problem got the lowest adjustment score; and of the eight children she listed as having showed problems at the beginning of the school year eight months previously, all had below average adjustment scores ranging from −30 to −10. The validity is further confirmed by the internal consistency of the results which corresponds to the consistency of the personality. Only two children had minus 10 in one aspect of their personality and plus 10 in another.

(3) *Social Adaptability Score*: 3 indicates high social adaptability and zero low social adaptability. These scores were calculated on the basis of three school reports covering the child's behavior over a period of six months. One point was given for each time the child was reported working and playing with other children in the manner approved by the kindergarten. Thus the range of individual scores was 3 to zero.

(4) Information based on ratings of kindergarten teacher.

(5) Information based on questionnaire filled out by parents.

(6) Information based on data collected during an interview with the mother.

(7) Information about five cases is missing.

TABLE IV. THE PERCENTAGE OF EACH FEEDING PATTERN GROUP HAVING OTHER FEEDING EXPERIENCES

	BREAST FEEDING				SCHEDULES			WEANING				REACTIONS				MIXED GROUPS	
	NEVER	ABORTIVE	SUPPLEMENTED	SUCCESSFUL	RIGID	LESS RIGID	FLEXIBLE	EARLY	LATE	UNHELD	SUDDEN	FEEDING RESISTANCE	FORMULA REACTIONS	WEANING REACTIONS	OTHER REACTIONS	LESS RIGID-SUPPLEMENTED	NO TRAUMA
Breast Feeding																	
Never	100	0	0	0	50	0	33	33	67	0	17	50	17	17	17	0	33
Abortive	0	100	0	0	63	0	25	50	50	0	0	25	38	0	38	0	50
Supplemented	0	0	100	0	33	50	17	50	50	33	17	0	17	33	50	50	17
Successful	0	0	0	100	33	67	0	33	67	33	33	0	0	67	0	0	0
Schedules																	
Rigid	27	45	18	9	100	0	0	64	36	9	18	36	45	9	36	0	9
Less rigid	0	0	50	33	0	100	0	17	83	33	17	0	0	67	17	50	17
Flexible	40	40	20	0	0	0	100	40	60	0	0	0	0	0	20	0	80
Weaning																	
Early	20	40	30	10	70	10	20	100	0	10	20	30	20	10	40	10	20
Late	29	29	21	14	29	36	21	0	100	14	14	14	21	36	21	14	36
Unheld	0	0	67	33	33	67	0	33	67	100	0	0	33	33	33	33	0
Sudden	25	0	25	25	50	25	0	50	50	0	100	25	0	75	25	0	0
Reactions																	
Feeding resistance	60	40	0	0	80	0	0	60	40	0	20	100	20	20	60	0	0
Formula reactions	20	60	20	0	100	0	0	40	60	20	0	20	100	0	60	0	0
Weaning reactions	17	0	33	33	17	67	0	17	83	17	50	17	0	100	33	17	0
Other reactions	14	43	43	0	57	14	14	57	43	14	14	43	43	29	100	14	0
Mixed Groups																	
Less rigid-supplemented	0	0	100	0	0	100	0	33	67	33	0	0	0	33	33	100	33
No trauma	29	57	14	0	14	14	57	29	71	0	0	0	0	0	0	14	100

TABLE V. THE PERCENTAGE OF EACH FEEDING PATTERN GROUP HAVING CERTAIN ENVIRONMENTAL INFLUENCES

	ONLY CHILD	FIRST CHILD	SECOND AND SUBSEQUENT CHILD	UPSET HOME	MOTHER NERVOUS	MOTHER SEPARATION	EARLY URINE TRAINING	FONDLY TALKING MOTHER	SPANKING
Breast Feeding									
Never	50	0	50	67	33	50	33	50	67
Abortive	63	25	13	25	75	25	38	38	25
Supplemented	17	83	0	83	50	17	17	50	67
Successful	0	67	33	33	67	0	0	67	67
Schedules									
Rigid	73	18	9	45	73	18	36	36	55
Less rigid	0	83	17	67	33	17	17	33	67
Flexible	0	40	60	60	20	40	20	80	40
Weaning									
Early	60	30	10	50	60	30	30	40	50
Late	21	50	29	57	50	21	21	50	57
Unheld	0	67	33	67	67	0	33	33	100
Sudden	50	50	0	75	75	25	0	50	75
Reactions									
Feeding resistance	100	0	0	40	60	40	40	20	60
Formula reaction	60	20	20	40	60	20	40	20	60
Weaning reaction	33	50	17	83	50	33	0	33	67
Other reactions	57	43	0	57	71	43	14	14	57
Mixed Groups									
Less rigid-supplemented	0	100	0	67	33	33	33	33	67
No trauma	14	43	43	43	43	43	14	71	14

Only Child—The only living child.

First Child—The oldest living child.

Second or Subsequent Child—The child with an older living sibling.

Upset Home—Environmental disturbances during the child's infancy, such as the father being away in service, or living unhappily with in-laws.

Mother Nervous—The mother reported herself nervous with the child at first.

Mother Separation—Mother and child separated six or more hours a day over a long period.

Early Urine Training—Urine training started before 1 year of age.

Fondly Talking Mother—The mother talked about her child in the interview in a fond, approving way.

Spanking—When both parents spanked rarely, or one parent spanked more than rarely.

TABLE VI. THE PERCENTAGE OF FIRST AND ONLY CHILDREN HAVING CERTAIN FEEDING EXPERIENCES

	ONLY CHILDREN* 9 CASES (%)	FIRST CHILDREN† 10 CASES (%)
Never or abortive breast feeding	89	20
Supplemented or successful breast feeding	11	70
Rigid schedule	89	20
Less rigid and flexible schedule	0	70
Early weaning	67	30
Late weaning	33	70
Feeding resistance	56	0
Formula reactions	33	10
Unheld bottle	0	20
No trauma group	11	30

*Only living child.

†Oldest living child.

adult suggestions and often needed reminding to do routine things. They did not take responsibility well, and all had a tendency to show off and act silly. None had indifferent appetites in childhood, and all had persistent sucking habits.

Reactions Groups.—Very little difference was found between the feeding reactions groups and the total group. The feeding resistance group all liked to play with older children, and daydreamed less than the total group. All of the formula reactions group liked to show off and act silly. They took responsibility well, but had persistent sucking habits. The weaning reactions group resisted adult suggestions and all of them had indifferent appetites in childhood.

Mixed Experience Groups.—The children who were fed on a less rigid schedule combined with supplemented breast feeding showed the least desirable behavior of any group studied. The group who experienced no feeding traumas tended to show more desirable behavior than the total group, although the difference was not consistent or marked.

Table IV shows how the feeding patterns were interrelated. For instance, rigid schedules were more common among those children who had little breast feeding.* Feeding resistance and formula reactions occurred exclusively among those on rigid schedules. Weaning reactions, late weaning, and longer breast feeding are interrelated.

*There is a good physiological reason for this. The sight or sound of an unsatisfied baby is likely to set off the let-down reflex in a lactating woman. This makes her breast feel heavy and ready for suckling. Thus she has a physiological as well as psychological reason for ignoring rigid scheduling.

Tables V and VI show how feeding experiences were related to other factors in the environment. For instance, upset home environment was much more common among the never and the supplemented groups than among the abortive and the successful groups.

DISCUSSION

There appears to be no simple explanation for the relationships found here. There are at least seven factors which might enter into the occurrence of the relationships. These are:

1. Chance.
2. A direct causal relationship.
3. The influence of related feeding experiences.
4. The attitudes and personality of the mother.
5. The attitudes and personality of the child.
6. Environmental influences.
7. Physical factors such as diet and heredity.

The law of chance is undoubtedly a factor in the relationships found in this exploratory study. The advantage of an exploratory study is that it can be wide in scope, and can investigate a phenomenon with the minimum of preconceived limiting assumptions. The limitations must also be recognized. Due to the large number of factors studied, some decided trends can be expected to occur by chance. The exploratory study can only open new avenues of thinking which must be validated or discarded by narrower studies on larger samples.

Evidence of a direct causal relationship is difficult to see in the results of this study. If feeding experience it-

self were a strong causal factor influencing later behavior, one would expect to find some direct relationship between the amount or degree of the experience and later behavior. However, this study found that the abortive breast fed group was quite similar to the successful breast fed and that both the rigid and flexible groups had more desirable behavior than the less rigid group. This is in keeping with the breast feeding studies of Childers and Hamil,[8] Hoefer and Hardy,[10] Maslow and Szilagyi-Kessler,[13] and Pearson,[14] all of whom have found a curvilinear relationship. Both Peterson and Spano[18] and Holway[11] looked only for linear relationships. Holway working with only seventeen children found high linear correlations; but Peterson and Spano found no significant evidence of such a linear relationship.

Second, if feeding experiences were strong causal factor in determining later behavior one would expect the same sort of behavior to occur among widely different groups who had happened to have the same sort of feeding experience. No such evidence has been found. For instance, Maslow and Szilagyi-Kessler in a study on Brooklyn College students found that those with the highest security scores on a security-insecurity inventory were those breast fed for a year or more or for less than three months, while Hoefer and Hardy working with Illinois school children found that those completely breast fed four to nine months had the most desirable mental and physical ratings. The small studies of Trainham[9] and Escolona[9] on feeding schedules indicate similar variation from group to group. Trainham found that the self-regulated children were more advanced in development; Escolona found them less advanced.

One important exception to the above generalizations must be noted. There is evidence that some direct relationship does exist between sucking activity and feeding time. Levy,[12] Roberts,[15] and this study working on very different groups found the same general sort of relationship.

However, in general, the relationships between early feeding experience and later behavior appear not only to be curvilinear but different in nature from group to group. This indicates that the cause and effect relationship between early feeding and later behavior is probably not a very strong one, and that other reasons for the relationship should be examined.

Perhaps if more emphasis in investigations had been placed on total feeding experience rather than on isolated factors, a stronger relationship, one more suggestive of cause and effect, might have been found. Table IV shows that weaning reactions to giving up the bottle occurred mostly in those who had had considerable experience with breast feeding previously. The behavior of the less rigid schedule group seemed to be related to the type of breast feeding they had. Of the three who had supplemented breast feeding on a less rigid schedule, all changed their behavior as adults approached, and all were unpopular. Of the two who had successful breast feeding on a less rigid schedule, neither changed their behavior as adults approached, and both were especially sought after as playmates by other children.

There is considerable evidence for the belief that attitudes of the mother are an important factor involved in the relationship between early feeding and later behavior. It is generally accepted that the attitudes of the mother can have a tremendous influence on the behavior of the child. It is not so generally realized that these same attitudes influence the type of feeding the child receives. For instance, the ability to enforce a rigid schedule might indicate a generalized commanding attitude on the part of the mother. Table III shows that the children fed on rigid schedules were definitely more likely to lead through giving commands than the other schedule groups. Perhaps this was an imitation of their mothers.

Presumably on the average the mother who goes on to have more than one child has a different attitude toward her first child than the mother who does not choose to have more than one child. Table VI shows that only children experienced decidedly less breast feeding, more rigid schedules, and earlier weaning and more feeding resistance than first children. Table V shows that children who experienced flexible schedules, successful breast feeding and no feeding traumas had the highest proportion of fondly talking mothers.

Other investigations show similar relationships between maternal attitudes and infant feeding. Newton and Newton found in a study of ninety-one mothers, all of whom attempted to breast feed, that 74 per cent of those who expressed a wholehearted desire to breast feed had enough milk to do so without supplementation as compared with 35 per cent of those who expressed indifference or ambivalence.[19] Freeman, in a study of 200 problem children, found that the woman who ended up with more children was more likely to breast feed her first longer.[20]

The difference between the breast feeding groups becomes meaningful when thought of in terms of mother's attitudes toward child care. A study of Tables IV and V reveals that two kinds of child care seemed to be prevalent in this group of mothers which leads to the following speculations: The biological type of mother preferred to breast feed for some time, and avoided the use of rigid schedules. When such a mother was upset and nervous, she failed to have enough milk to completely satisfy her baby because her let-down reflex was probably inhibited.[21, 22] Thus the child of an upset biological type mother was likely to fall into the supplemented feeding group. (Table V.) The modern urban type mother preferred bottle feeding and rigid schedules. If she was particularly conscientious for the welfare of her child she made a brief attempt to breast feed because she had heard breast feeding was better, but she soon failed and stopped breast feeding altogether because she had no deep emotional desire to breast feed.[19] One would expect the conscientious modern urban type mother and the placid biological type mother to have the best adjusted children, and this is just what was found.

In terms of mother's personality differences, it is not surprising to find none of the best or the worse adjusted children in the rigid schedule group. Only the conscientious, responsible mother can stick to an absolutely rigid

schedule, day in-day out, however inconvenient the time may occasionally be for her. Nor is it surprising to find no markedly well-adjusted children in this group. Evidence points to the fact that most newborn infants perfer more frequent feedings than the four-hour schedule on which these children were placed.[23] Thus the mother who sticks to a rigid schedule is likely to be the type of mother who is more sensitive to other factors than to her child's inner needs.

The important thing to note is that the type of feeding can mean a different thing to each mother depending on her individual attitudes and her culturally influenced standards of behavior. Flexible feeding schedules to one mother may mean the best way of expressing her devotion to her child's needs. However, another mother stated in the interview: "Oh, I fed my next child on a much more flexible schedule. He had to fuss much more for his feedings." Maslow pointed out that a possible reason for his finding the lowest security scores among those breast fed a few months may be due to the fact that he was working with mostly second generation Americans. One can speculate that those mothers who did not breast feed were trying to do the best for their child by initiating the new American ways: those who breast fed longest were doing what their old culture deemed best for the child. Those who breast fed a few months were those who had a conflict between old ways and new.

If the type of feeding experience has different meaning to different mothers because of cultural and personal differences, and if she chooses the feeding experience for her child that best expresses her attitude towards him, then we would expect to get just what has been found in this and other investigations; i.e., a strong but curvilinear relationship between early feeding and later behavior that varies tremendously from group to group, and also shows some variation within the group.

The personality of the child is another factor that probably influences both feeding experience and later behavior and thus contributes to the causation of the relationship between early feeding experience and later behavior. Table III shows that children who were persuaded to give up their bottle before one year of age were also more likely to accept adult suggestions at kindergarten age, while many of the children who had weaning reactions were still resisting adults' suggestions at kindergarten age. All of the group who had formula reactions in their early infancy liked to show off and act silly at kindergarten age.

There are many other possible factors that may contribute to the relationship between early feeding and later behavior. The influence of the father's attitude, the home, and neighborhood environment could be expected to influence the type of feeding experience the child receives and also his later behavior. For instance, the preference of the feeding resistance group for older children might well be due to the fact that they were all only children and thus used to more mature behavior. Dietary and hereditary factors are hard to assess. However, they should not be forgotten as possible influences determining infant feeding behavior of the mother,

and also the later behavior of the child.

SUMMARY

The many possible causes of the relationship between infant feeding experience and later behavior have been discussed. Research papers on the subject have been cited, and the results of an exploratory study done in great detail on twenty-four kindergarten children have been reviewed.

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AN EVALUATION OF A CARBOHYDRATE-PHOSPHORIC ACID SOLUTION IN THE MANAGEMENT OF VOMITING

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THE great majority of cases of vomiting are functional, as in epidemic vomiting, regurgitation in infants, motion sickness, nausea and vomiting of early pregnancy, etc. When vomiting is the result of an organic condition, such as pyloric stenosis or a brain tumor, it is obvious that the emesis can be relieved only by the removal of the organic cause. The term "epidemic vomiting" has been applied to a seasonal disease of epidemic character with vomiting as its most prominent symptom. Other designations include: intestinal "flu," intestinal grippe, gastric influenza, acute infectious gastroenteritis,[1] seasonal gastroenteritis,[2] winter vomiting, and Spencer's disease.[3] It is most frequently seen in infants and children, but may also occur in adults.

THEORETICAL AND EXPERIMENTAL BACKGROUND

Epidemic vomiting is usually a self-limited disorder and not fatal. Little is known of its etiology, but it has been noted that many patients exhibit disturbances of carbohydrate metabolism,[4] as indicated by glycosuria and prolonged elevation of blood-sugar levels after glucose administration. This clinical observation, plus the fact that parenteral administration of carbohydrate often results in cessation of the vomiting, led us to suspect that whatever was responsible for epidemic vomiting perhaps interfered with carbohydrate utilization. However, since oral carbohydrate was not eminently satisfactory, we speculated as to whether there was not some factor necessary for correcting deranged carbohydrate metabolism other than simple oral carbohydrate therapy. Recalling the fact that phosphate groups play an important role in carbohydrate metabolism,[5] we decided to test whether an orally administered carbohydrate-phosphoric acid solution would restore elevated blood-sugar levels to normal and have a corrective effect on the vomiting. Since the mechanism of vomiting involves contraction of the pars pylorica as well as the coordinated muscular action of the esophagus and abdominal wall, it was recognized that any orally administered preparation given to control vomiting must prevent contraction of the pars pylorica to be effective.

Our next step, therefore, was to see whether the oral preparation would produce any effect on the contraction rate of gastrointestinal smooth muscle. This was done experimentally by observing the behavior of isolated strips of rabbit gastrointestinal muscle, 1 to 1½ inches long and sectioned to include a portion of the pars pylorica. A sustained reduction in contraction rate was obtained without complete loss of tone, and with a marked reduction in amplitude. (Fig. 1.) The results also suggested that changes in pH

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might play an important part in the effect obtained. Our experiments repeatedly confirmed the well-known fact that an increase in acidity is usually accompanied by increased inhibition of smooth muscle contraction in the gut. It became evident that in order to produce the desired result we had to keep the test solution within an optimal pH range. These findings are to be reported in a separate publication.

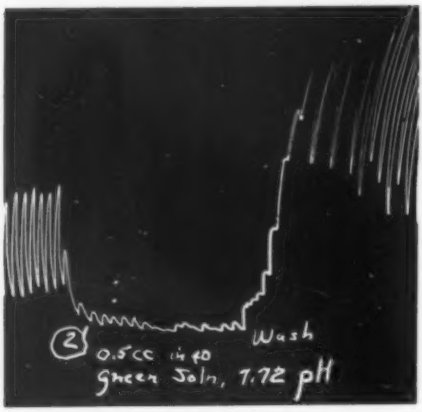

Fig. 1.

CLINICAL FINDINGS

Since it was concluded that the carbohydrate-phosphoric acid solution might exhibit the same effect on smooth-muscle motility in vivo after oral administration, it was decided to administer the solution to patients afflicted by vomiting. For the past eighteen months, we have been working with a clinically satisfactory carbohydrate solution* made with invert sugars and phosphoric acid and stabilized at an optimally adjusted pH. In addition to our use, the preparation was distributed among a number of practicing pediatricians, who were asked to give it in 5 c.c. doses, undiluted, at intervals of fifteen minutes for a total of four doses. In some older children, or in those who had been vomiting for a long period, the dose was increased to 10 or 15 c.c. at the same interval. In addition, the solution was employed in two patients who were admitted to the University Hospital seriously dehydrated from protracted vomiting. (Case reports on these patients are given later.)

The patients selected for testing the clinical effectiveness of the carbohydrate-phosphoric acid solution include 172 cases diagnosed as epidemic vomiting, 43 cases of regurgitation of infants, 17 cases of toxic vomiting or vomiting associated with acute infections, 11 cases of motion sickness, and 3 cases involving stenosis of the pylorus. The pediatricians kept in mind the fact that in order to demonstrate effectiveness, the solution must be given undiluted so that there will be no alteration in its pH before reaching the stomach, and, for the same reason, should not be followed immediately by water, milk, or other liquids.

The treatment in epidemic vomiting was supplemented by maintaining the patient on a low-fat, high-carbohydrate, low-residue diet, and elimination of milk and citrus fruits for a twenty-four-hour period. Administration of the solution in regurgitation of infants was restricted to those infants who had failed to respond favorably to phenobarbital, atropine, or other drugs. The dosage used was 2.5 to 5 c.c. fifteen to thirty minutes before feedings. The

*The product used was Emetrol which was furnished through the courtesy of Kinney & Company, Columbus, Ind. Emetrol is a solution of invert sugars (57 per cent total solids) and orthophosphoric acid with suitable stabilizers and flavors. Hydrogen ion concentration is controlled to a pH of 1.5 to 1.6. Invert sugars syrup 75 Gm., glycerin USP 12.5 Gm., methylparaben USP 0.2 Gm., phosphoric acid USP 0.3 Gm., flavor 0.1 Gm. in 100 c.c. distilled water.

TABLE I. RESULTS OF ADMINISTRATION OF CARBOHYDRATE-PHOSPHORIC ACID SOLUTION

CONDITIONS	NUMBER OF CASES	VOMITING CONTROLLED	NOT CONTROLLED
Epidemic vomiting	172	172	0
Regurgitation of infants	43	29	14
Toxic vomiting	17	15	2
Motion sickness	11	11	0
Pyloric stenosis	3	0	3

patients with motion sickness were children who regularly experienced nausea and vomiting as a consequence of automobile or trolley-car riding. The initial dose (5 to 10 c.c.) was administered before starting a trip and repeated at hourly intervals if travel was of extended duration. Table I presents the results obtained by administering the carbohydrate-phosphoric acid solution in the conditions mentioned. The vomiting of epidemic character responded to the therapy in every case, often with a single dose. Regurgitation of infants ceased or was modified in 67 per cent of cases. The regurgitation did not return for a period of two weeks after withdrawal of the solution, except in two cases requiring continued administration to prevent regurgitation. Motion sickness was effectually prevented in every case of a small series; more clinical reports are desirable. As was expected, the vomiting of pyloric stenosis did not respond. The solution does not correct vomiting or regurgitation due to obstruction or other organic factors nor does its use eliminate the need for correcting improper feeding methods.

CASE REPORTS

(Epidemic Vomiting)

CASE 1.—E.M., an 8-year-old white girl, was admitted to the University Hospital in December, 1949, with a history of vomiting for the three preceding days. The history was noncontributory in all other respects. At the time of her admission, physical examination showed only a profoundly dehydrated child. Blood sugar at the time of admission was 148 mg. per cent; the CO_2 content was 17 meq.; the blood chlorides were 90 meq.; the blood sodium 131 meq.; and potassium 5.5 meq. The carbohydrate-phosphoric acid solution was given in doses of 15 c.c. every fifteen minutes for four doses. All doses were retained and this, we were told, was the first liquid or food the child had retained since the onset of the illness. At the end of one hour the blood analysis was repeated and the following results were obtained: blood sugar 94 mg. per cent; CO_2 content 19 meq.; blood chlorides 95 meq.; blood sodium 132 meq.; and blood potassium 5.55 meq. After these studies the patient was given parenteral fluids and she made an uneventful recovery.

CASE 2.—D. F., a 19-month-old male infant, was admitted to the University Hospital with a history of vomiting for the four preceding days. The remainder of the history was noncontributory. The physical examination except for the signs of dehydration was essentially negative. The biochemical results obtained at the time of admission were as follows: blood sugar 99 mg. per cent; CO_2 content 14 meq.; blood chlorides 120 meq.; blood sodium 150 meq.; blood potassium 4.5 meq. The patient was given 15 c.c. of the carbohydrate-phosphoric acid solution at fifteen-minute intervals for a total of four doses. All doses were retained. At the end of the period, the biochemical results were as follows: blood sugar 62 mg. per cent; CO_2 content 18 meq.; blood chlorides 108 meq.; blood sodium 150 meq.; and blood potassium 3.5 meq. Parenteral glucose was then admin-

istered and the patient was discharged forty-eight hours later.

It is significant that in these patients *no further vomiting occurred after the institution of therapy.* It is also interesting to note the effect on blood-sugar levels which in both cases were returned to lower levels. Biochemical studies are now in progress to obtain additional data on this correlation. It is not suggested that oral therapy replace parenteral administration of fluids for the correction of dehydration.

DISCUSSION

The use of an oral carbohydrate-phosphoric acid solution to stop vomiting represents a novel therapeutic approach. The results from its use strongly suggest that it is effective in restoring cellular utilization of carbohydrate by repairing a defect in the continuity of carbohydrate metabolism. This apparently requires the use of a phosphoric compound under optimal hydrogen-ion concentrations probably necessary for zymogen activation. Experimental and clinical studies to provide further confirmation of these hypotheses will be reported in a later paper. The therapy described offers a simple, effective method of controlling vomiting in many common conditions. The absence of toxic or unpleasant side effects in the observed series increases the value of this solution to the practitioner.

SUMMARY

1. Results of a preliminary study of the effect of a carbohydrate-phosphoric acid solution on isolated rabbit gastrointestinal-muscle strips, including sections of the pars pylorica, are presented.

2. Clinical trial of the oral preparation was made in 246 cases of nausea, vomiting, or regurgitation in infants and children.

3. Cessation of vomiting occurred in 100 per cent of 172 cases of epidemic vomiting. Two cases reports are given.

4. Of 43 infants suffering from regurgitation, 29 responded favorably; these cases had previously failed to respond to atropine, phenobarbital, or other preparations.

5. Fifteen of 17 patients with toxic vomiting responded favorably.

6. Motion sickness was prevented in 100 per cent of 11 children regularly subject to nausea when traveling in vehicles.

7. Three patients with vomiting due to pyloric stenosis did not respond.

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ELECTROCARDIOGRAPHIC CHANGES OCCURRING DURING THE COURSE OF REPLACEMENT TRANSFUSIONS

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THE use of citrated whole blood in replacement transfusions should result in a marked reduction of serum ionized calcium. This was first recognized by Wallerstein in 1947[1] when he advised the adminstration of 1 Gm. of calcium gluconate, given in divided doses, during the course of the transfusion. The majority of workers have adopted either this technique or that of giving the same amount of calcium gluconate slowly at the conclusion of the procedure. Aside from the infrequent appearance of muscle tremors, there has been no evidence of a deficiency of ionized calcium produced during the replacement transfusion.

With the electrocardiographic changes of hypocalcemia well established, serial electrocardiograms were taken during the course of replacement transfusions: first, to obtain definitive evidence of a reduction in ionized calcium during the procedure; and second, to see if this was satisfactorily corrected by the intravenous injection of 1 Gm. of calcium gluconate at the conclusion of the transfusion.

METHODS AND RESULTS

Studies of six patients are here reported. All were between 4 and 26 hours of age, weighed between 2,065 and 4,775 grams, and received from 480 to 580 c.c. of citrated blood over 70- to 130-minute periods. At the conclusion of the transfusions, each patient received 10 c.c. of 10 per cent calcium gluconate intravenously over a two- to four-minute period. Electrocardiograms employing the three augmented unipolar as well as the three standard limb leads were taken in all the patients before and after the transfusions and during and immediately after the calcium administration. Records were obtained in three patients midway through the transfusion, and in four the records were repeated fifteen to sixty minutes after the calcium had been given. Total serum calcium[2] and serum proteins[3] were measured in four patients, and pH and carbon-dioxide combining power[4] in one patient, specimens for all determinations being obtained before and after the transfusion and a minute after the calcium had been given.

Electrocardiographic changes during the exsanguination replacement procedure were noted in all six patients. In four there were marked fine skeletal muscle tremors, detectable clinically in only one instance, which obscured the P and T waves and prevented measurement of electrical systole (Fig. 3). In the other two patients there was a marked prolongation of electrical systole, with K (calculated according to the formula of Bazet $K = QT/\sqrt{RR}$) increasing from 0.422 and 0.428 to 0.526 and 0.512, respectively. That this increase in Q-T was due to a

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prolongation of the ST segment is graphically illustrated in Fig. 1. In both of these patients there was a slight decrease in the amplitude of the T waves in Leads I and aV_L without any change in the configuration of the QRS.

Of the records taken midway through the transfusion, two revealed prolongation of K, fine skeletal muscle tremors appearing subsequently in just one of these patients (Fig. 2). The third record revealed no increase in K at the half-way point with marked skeletal muscle tremors appearing later without any preceding prolongation of electrical systole. During the transfusion there was no change in any of the records in the duration of the P-R interval and QRS complex or in electrical position. In two patients there was a significant increase in heart rate of twenty or more beats per minute.

During the intravenous administration of calcium gluconate, there was a dramatic reversal of the electrocardiographic changes. The muscle tremors were markedly diminshed after 2 to 3

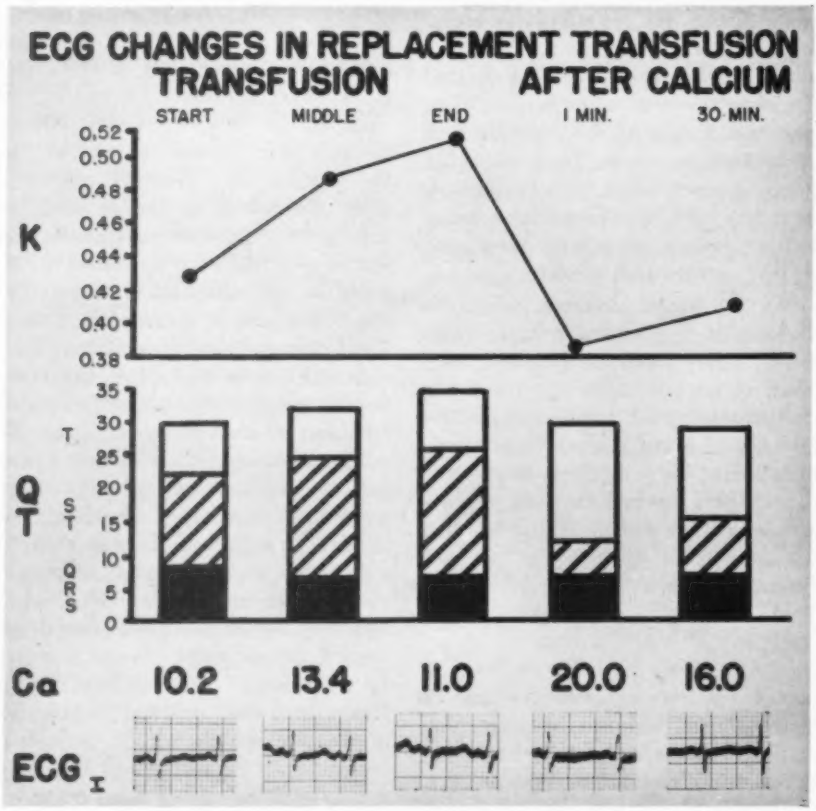

Fig. 1.—Graphic summary of the changes in K and the duration of the S-T segment and the T wave during the procedure. The relationship between these changes and the serum calcium is discussed in the text.

c.c. and were abolished after 7 to 8 c.c. had entered the vein (Fig. 3). The prolonged Q-T returned to normal in the other two patients after 3 to 4 c.c. had entered.

In the records taken after all the calcium had been absorbed, there was a constant reduction in heart rate, varying between twenty-four and thirty-four beats per minute (Fig. 3). Sinus arrhythmia was noted in five cases, premature auricular beats in two (Fig. 3). There was no change in the QRS interval although P-R lengthened in two (0.12 to 0.14). In all patients there was a reduction in K to below the value

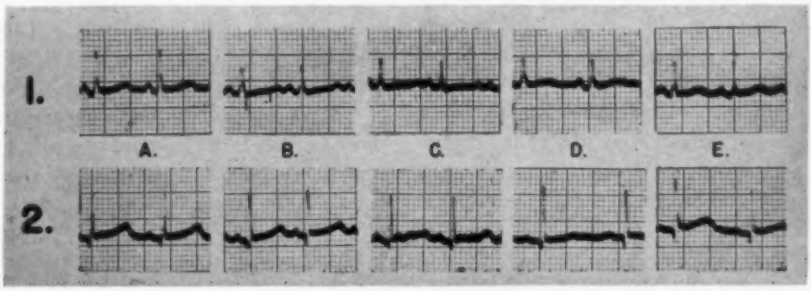

Fig. 2.—Effects of transfusion. *A*, Start of the transfusion; *B*, midway through the transfusion; *C*, end of the transfusion; *D*, one minute after calcium administration, and *E*, thirty minutes after calcium administration.

1. Lead II—note the prolongation of Q-T by increase in the S-T segment.

2. Lead II—note the increase in K prior to the appearance of fine skeletal muscle tremors. *D* reveals decrease in the height of the T wave with restitution of the original pattern in *E*.

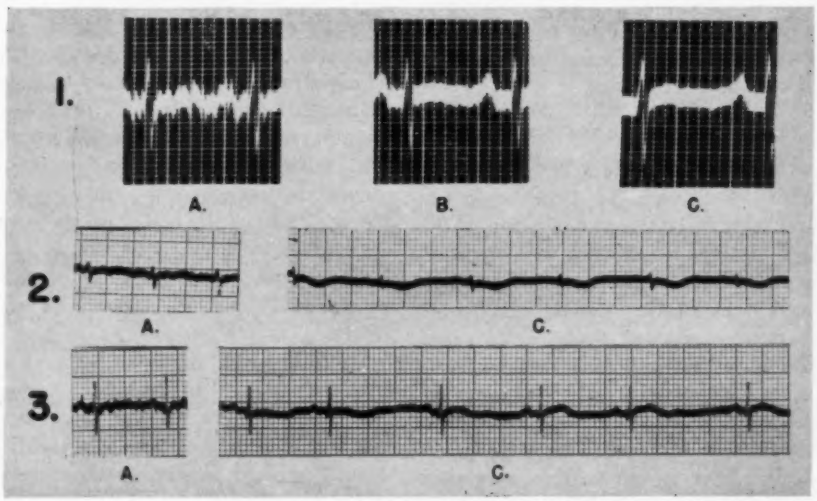

Fig. 3.—Effects of intravenous calcium. *A*, At the end of the transfusion; *B*, after 0.2 Gm. of calcium gluconate, and *C*, after 1.0 Gm. of calcium gluconate.

1. Lead II—abolition of skeletal muscle tremors.

2. Lead I—reduction in heart rate.

3. Lead III—production of sinus arrhythmia.

at the start of the procedure, the average change being from 0.423 to 0.386, the degree of reduction varying from 0.011 to 0.065. In the four records in which accurate measurements of the duration of S-T and T were possible, there was a significant reduction in the duration of the ST segment in three, with increase in the T-wave duration in two (Fig. 1). In four of the six cases the T waves that had been upright in Leads I and aV_L at the start of the procedure were isoelectric or inverted immediately after the calcium had been given, without any change in the character of the QRS complexes (Fig. 1).

There were no significant changes in total serum calcium during the course of the transfusion, two patients showing slight elevations, two slight decreases. After the intravenous administration of calcium gluconate, all showed a marked rise in the serum calcium, averaging a 70 per cent increase. Total serum proteins and pH and CO_2 showed no fluctuations.

DISCUSSION

Carter and Andrus in 1922[5] and White and Mudd in 1929[6] were the first to describe the prolongation of the Q-T interval in patients with hypocalcemia. That the prolongation was primarily and characteristically in the ST segment was noted first by Marzahn[7] and since has been confirmed by many other observers.[8-12] The changes in the configuration of the ST segment and the T wave that have been described have been inconstant. In some of the records reproduced of patients with hypocalcemia, fine muscles tremors are discernible, in some instances vanishing after the administration of calcium, but no comment was made about them.[8, 10, 13]

In addition, the electrocardiographic changes of hypercalcemia have been well described, both in experimental animals and in man. In 1939, Hoff and collaborators[14] described a reproducible sequence of events after intravenous calcium administration in dogs, characterized initially by the appearance of bradycardia and A-V block. This was followed by a period of increased automatism marked by increase in rate, appearance of extrasystoles, tachycardia, and, in about one-half the animals, a fatal ventricular fibrillation. The animals surviving this period succumbed to an ensuing depression with sinus bradycardia followed by cardiac arrest. The electrocardiograms during this time showed increase in the P-R and QRS intervals, shortening of Q-T due to a decrease in the S-T segment with apparent decrease in the duration and height of the T wave. Following the administration of intravenous calcium in man, Berliner[15] and Clarke[16] both noted bradycardia and sinus arrhythmia initially, followed in some instances by either sinus arrest or A-V block. Tachycardia and ventricular extrasystoles were noted in one patient. Berliner noted a shortening of Q-T, primarily in the S-T segment, with a decrease in the amplitude of the T wave in Lead II. In two patients with hypercalcemia described by Kellogg and Kerr,[17] there was an increase in the P-R and QRS intervals in addition to Q-T changes similar to those previously described.

The electrocardiographic changes which we observed during the actual exsanguination replacement procedure

—the fine skeletal muscle tremors, the prolongation of the Q-T interval by an increase in the duration of the S-T segment and the decrease in the amplitude of the T wave are the classical changes of hypocalcemia. The failure of the serum calcium measurements to reflect this deficiency is to be expected as this determination measures only total calcium, including ionized calcium as well as the unionized calcium bound to protein and citrate. The dramatic reversibility of these changes following calcium administration supports the contention that these changes were due to a reduction in serum ionized calcium.

There was no correlation between the type and degree of the electrocardiographic changes noted and the ages and weights of the patients or the amount and the duration of the transfusion. It is interesting to note that while two patients showed prolongation of the Q-T prior to the development of the skeletal muscle tremors, there was one who showed the muscle tremors as the first electrocardiographic manifestation of the deficiency in serum ionized calcium.

The electrocardiographic changes observed immediately after the calcium administration are identical with those previously described in the initial stages of hypercalcemia. Of these changes, the bradycardia, sinus arrhythmia, and premature beats were transient in their appearance, and disappeared in all a few minutes after the administration of the calcium. The lengthened P-R intervals, shortened electrical systole, and inverted T waves returned to normal fifteen minutes after the calcium had been given. The severity of these changes was primarily related to the rapidity of the calcium injection and emphasizes the importance of giving the calcium more slowly than has been our custom. At least five minutes probably should be required. The restitution of the electrocardiogram by 1 Gm. of intravenous calcium appears to indicate that this is an adequate amount for a 500 c.c. replacement transfusion, regardless of the size of the baby.

SUMMARY

Serial electrocardiograms taken during the course of replacement transfusions in six patients revealed:

1. Development of changes characteristic of hypocalcemia.

2. Reversal of these changes by the intravenous administration of 1 Gm. of calcium gluconate.

3. Appearance of changes of hypercalcemia when the calcium administration required less than five minutes.

The detection of a reduction of ionized calcium by the electrocardiogram in the presence of a normal or elevated serum calcium is demonstrated.

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RESULTS OF HISTOPLASMIN SKIN TESTING IN CHILDREN FROM THE ST. LOUIS, MO., AREA

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SINCE the first cases of histoplasmosis were observed and described by Darling[2] in the early part of this century, a great deal remains to be learned concerning the epidemiology, prevention, and treatment of this disease. In recent years, skin tests with histoplasmin by Christie and Peterson,[1] Furcolow,[3] and Palmer[4] have disclosed a high percentage of positive reactions, which is a fact that is difficult to explain. In an effort to gain additional information concerning this interesting problem, a study was undertaken to learn the status of reactions to histoplasmin in infants and children.

The present report summarizes the results obtained from a series of 500 histoplasmin skin tests done on infants and children in St. Louis, Mo. Special attention was given to children under 3 years of age, and this age group constitutes the majority of patients presented.

MATERIAL AND METHOD

The material used for intradermal testing was a filtered broth culture of *Histoplasma capsulatum*.* The stock material was diluted 1:1,000 with normal saline solution.

New one milliliter syringes and No. 26 gauge needles were used. These were cleaned and autoclaved after each use. The skin test was done by injecting intradermally 1/10 ml. of the 1:1,000 dilution of histoplasmin on the volar aspect of the right forearm. The tests were read forty-eight hours later.

The reaction was considered positive if the area of induration was 5 mm. or more in diameter, without regard for erythema.

*Obtained from M. L. Furcolow, M.D., of U.S.P.H. Unit, University of Kansas, Kansas City, Kan.

SUBJECTS

Between November, 1946, and May, 1947, 500 children admitted either to St. Louis Children's Hospital, St. Louis City Hospital, St. Louis County Hospital, or Homer G. Phillips Hospital were tested intradermally with histoplasmin. There was no selection of subjects with regard to diagnosis, race, or sex. Skin tests were done on patients admitted to the ward and semiprivate services. Subjects ranged in age from a few days to 15 years.

RESULTS

Seventy-three (14.6 per cent) of the 500 children skin tested in this series gave positive reactions to intradermal histoplasmin. A detailed tabulation for each age group is given in Table I. If these data are grouped for each three-year interval, a graph may be plotted, Fig. 1, which shows the rapid increase in incidence of positive reactions with the increase in age.

In an effort to gain additional information, more complete data were obtained on the last 310 children tested, of whom forty-three (13.9 per cent) showed positive skin reactions to histo-

TABLE I. HISTOPLASMIN SKIN TESTS

AGE IN YEARS	NUMBER OF PATIENTS TESTED	NUMBER SHOWING POSITIVE REACTION	PERCENTAGE SHOWING POSITIVE REACTIONS
0-½	124	1	0.8
½-1	53	2	3.8
1-2	49	1	2.0
2-3	36	1	2.8
3-4	43	3	6.9
4-5	27	7	25.9
5-6	35	10	28.6
6-7	12	2	16.6
7-8	20	6	30.0
8-9	17	7	41.1
9-10	17	6	35.3
10-11	13	4	30.8
11-12	12	6	50.0
12-13	14	8	57.1
13-14	13	4	30.8
14-15	15	5	33.3
Totals	500	73	14.6

plasmin. In this group the data were tabulated according to sex, race, diagnosis at time of discharge, and according to the geographic location of the patients' homes.

In this group 182 males were tested and thirty-one (17.1 per cent) showed positive reactions to histoplasmin. One hundred twenty-eight females showed twelve (9.3 per cent) positive reactions.

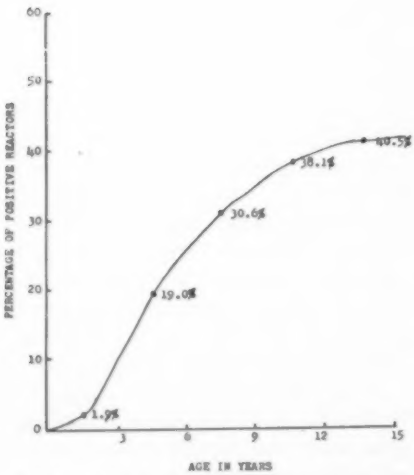

Fig. 1.—Percentage of positive histoplasmin reactors for each 3-year age period.

Only twenty-five Negroes were tested, and three (12 per cent) of these had positive skin reactions.

A tabulation was made of discharge diagnoses in this group of 310 patients. An effort was made to correlate the incidence of acute and chronic disease with histoplasmin skin tests. Results are tabulated in Table II. Table III summarizes the types of chronic disease found in the thirty-one positively reacting patients.

The geographic location of the homes of the forty-three patients with positive histoplasmin reactions was determined. Of this group thirty patients (69.7 per cent) lived in rural areas or in a community of less than 5,000 people. The remaining patients lived in urban areas. For a comparison, the geographic location of the homes of 500 successive admissions to St. Louis Children's Hospital, during the period of this study, was determined.* This data revealed that 394 (78.8 per cent) came from cities or towns of more than 5,000 population, which is in striking contrast with that found in the histoplasmin-positive group.

*The large majority of patients in this study were from St. Louis Children's Hospital.

TABLE II. CHARACTER OF DISEASE DIAGNOSED ON THE FORTY-THREE PATIENTS WITH POSITIVE REACTIONS TO HISTOPLASMIN AND A COMPARISON WITH THE CHARACTER OF DISEASE DIAGNOSED IN THE 267 NONHISTOPLASMIN REACTORS, WITH PERCENTAGES FOR EACH GROUP

CHARACTER OF DISEASE	HISTOPLASMIN POSITIVE		HISTOPLASMIN NEGATIVE	
	NUMBER	PER CENT	NUMBER	PER CENT
Acute	8	18.6	194	72.7
Questionably Chronic	4	9.3	34	12.7
Chronic	31	72.1	39	14.6
Total	43	100.0	267	100.0

TABLE III. TYPE OF CHRONIC DISEASE FOUND IN THE THIRTY-ONE CHRONICALLY ILL, HISTOPLASMIN-POSITIVE PATIENTS SHOWN IN TABLE II.

TYPES OF CHRONIC DISEASE	NUMBER
Chest and upper respiratory disease of long standing	11
Chronic cardiac disease	5
Chronic gastrointestinal tract disease	3
Chronic genitourinary tract disease	6
Miscellaneous chronic disease	6
Total	31

TABLE IV. FINDINGS ON EXAMINATION OF THE CHEST X-RAYS OF THE EIGHTEEN HISTOPLASMIN-POSITIVE PATIENTS ON WHOM X-RAYS WERE AVAILABLE

REPORT OF CHEST X-RAY	NUMBER	PER CENT
Calcification of tracheobronchial lymph nodes as well as parenchyma	9	50.0
Peritracheal and hilar lymphadenopathy	5	27.8
Normal chest	4	22.2
Total	18	100.0

Chest x-rays were available on eighteen patients who had positive reactions to histoplasmin. None of these eighteen patients had a positive tuberculin skin test. The x-ray reports of this group of patients are summarized in Table IV. In only one instance in this series did a patient have both a positive histoplasmin test and a positive tuberculin skin test. No chest x-ray was available on this patient.

Of the 500 patients tested, 262 (52 per cent) were under 3 years of age. Because few studies on infants have appeared, the data for this group have been subjected to further analysis. Only five (1.9 per cent) of the children under 3 years of age were found to be histoplasmin positive. The youngest of these was 4½ months of age. None of the five patients with a positive histoplasmin skin test had positive tuberculin tests; four of them had chronic lung infection, and one had chronic renal disease. Chest x-rays of these five patients showed no evidence of calcification. All five were from homes in a rural community on a very small town.

DISCUSSION

The lower percentage of positive histoplasmin reactions (14.6 per cent) in this series as compared to Palmer's[4] study of adults in Missouri may be explained by the difference in age. From the data in Table I and Fig. 1 the percentage of positive reactions is shown to increase with age. Comparable studies in children by Furcolow,[3] working in the area around Kansas City, Mo., yielded results which were almost identical. Christie and Peterson,[1] studying children over 6 years of age

in Tennessee, showed a much higher incidence of positive reactions for the older age periods. Other studies have also shown marked variation in percentage of positive histoplasmin reactions for various geographic locations.

The higher incidence of positive reactions in males as shown in this series is a finding which was noted by Furcolow[3] also.

The fact that chronic disease occurred in 72.1 per cent of the positive histoplasmin reactors and in all patients with positive reactions under 3 years of age is a notable finding. In contrast, only 27.4 per cent of the nonhistoplasmin reactors were diagnosed as having chronic diseases.

Sixty-nine and seven-tenths per cent (69.7 per cent) of the positive reactors were found to reside in rural communities and in small towns. All of the positive reactors under 3 years of age resided in small towns or in rural areas. This was an interesting observation when it was found that 78.8 per cent of 500 routine admissions to St. Louis Children's Hospital during this same period of time were from urban areas of over 5,000 population. This would suggest that the agent or agents giving rise to positive histoplasmin reactions might be more prevalent in rural areas.

The reports of chest roentgenograms summarized in Table IV agree with many previous observations which have shown that a large percentage of pulmonary calcifications in patients are not associated with a positive tuberculin skin test nor with clinical evidence of active tuberculosis.

No patient in this series was considered to have, nor was diagnosed as having, clinically active histoplasmosis. This would suggest that a positive reaction to this skin test material represents an as yet unrecognized subclinical infection, that it gives cross reactions with other fungus infections as suggested by several studies, or that it is a nonspecific reaction.

SUMMARY

1. Histoplasmin skin tests were done on 500 children in the St. Louis, Mo., area.

2. The incidence of positive histoplasmin tests increases rapidly with age up to 10 years.

3. A higher incidence of positive skin tests in males was found.

4. Data on subjects under 3 years of age have been analyzed separately.

5. The high incidence of chronic disease among positive histoplasmin reactors is noted.

6. The rural locale of the homes of the large majority of positive histoplasmin reactors is observed.

7. The findings on chest roentgenograms of positive reactors are summarized.

We wish to express our appreciation to Russell J. Blattner, M.D., Professor of Pediatrics, Baylor University College of Medicine, Houston, Texas, for his suggestions and help in this study.

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PROGRESSIVE DIAPHYSEAL DYSPLASIA (ENGELMANN'S DISEASE)

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URBANA, ILL.

PROGRESSIVE diaphyseal dysplasia was first described as an entity by Engelmann in 1929.[1] In 1948, Neuhauser and co-workers[2] reported four additional cases and presented the first and only pathologic study of the involved bone to date. Sear in 1948,[3] Michaelis in 1949,[4] and later Stronge and McDowell[5] reported single cases of this unusual syndrome bringing the total of reported cases to eight. From reports in the literature it is evident that this type of bone dystrophy is of rare occurrence or is seldom recognized and diagnosed.

This unusual condition, sometimes reported as Engelmann's disease, occurs with equal frequency in both sexes and the age at time of first observation has varied from 4 to 28 years. The presenting symptoms have included a waddling gait, easy fatiguability, failure to gain weight, and pain in the lower extremities. Family history has been noncontributory except in the case of Michaelis where an unexamined sibling was reported to have an abnormal gait.

Physical examination has uniformly revealed poor nutrition and underdevelopment of the lower extremities except in a single reported patient. A waddling, wide-based gait was noted in six patients, knock-knees in two patients, and an "uncertain gait" in one instance. The intelligence of patients has been regarded as normal although there are no reports of psychometric studies. Elongation of the lower extremities and a lumbar lordosis was reported in three patients. Two patients demonstrated hyperactive deep reflexes and inconstant ankle clonus, another showed slightly diminished knee jerks, while a fourth had absence of one ankle jerk and both knee jerks. The remaining four patients were considered neurologically negative.

Laboratory tests have not been informative generally. Serology has been negative in all reported cases and all complete blood counts were within normal range. Calcium, phosphorus, and alkaline phosphatase studies revealed slight deviations from normal in only two instances; a slightly diminished serum calcium was noted in one patient and a slightly elevated phosphatase in another. Serum globulin was elevated in one instance.

Roentgen studies have revealed a symmetrical involvement of all long bones. Engelmann reported more distal involvement of the femur and humerus. Stronge and McDowell concurred with Engelmann that the involvement was located proximally in the tibia, fibula, radius, and ulna.

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Characteristic changes at the base of the skull have been observed in six patients; involvement of the clavicles has been noted in three cases, and changes in the innominate bones and scapulae have been described in single cases.

Roentgenographic changes in the long bones consist of fusiform osteosclerotic enlargement of the diaphyses with normal epiphyses and metaphyses. The cortices are generally thickened with increased though irregular density. Normal trabeculation is absent in the involved areas and a rather sharp demarcation exists between normal and pathologic bone.

The skull, when involved, has shown patchy thickening of the base, most marked in the anterior and middle fossae; occasionally the frontal bone has demonstrated similar changes.

Biopsy of the abnormal bone, as reported by Neuhauser and co-workers, has revealed a thickened periosteum. The cortex exhibits evidence of increased activity and eventual change to cancellous bone. Cancellous trabeculae are more narrowed than normal and the marrow is changed from the normal fatty type with occasional hematopoietic foci to a loose fibrous type with collections of mononuclear cells and small numbers of hematopoietic cells. Thickening of blood vessel walls to the point of obliteration of the lumina was observed. Vascular and marrow changes were interpreted as nonspecific.

Four patients had been followed for periods varying from three and one-half to seven years. While some degree of progression of the bony lesions was noted in younger patients, the clinical courses were essentially unchanged during the periods of observation.

An additional case of progressive diaphyseal dysplasia is reported here. The rarity of occurrence of this disease as indicated by reports in medical literature justifies the calling of attention to a single case. This patient was younger at the time of initial examination than any reported heretofore.

CASE REPORT

B. Y., a white female, was first seen by one of us (J. B. G.) on Nov. 17, 1948, at the age of 33 months. The family and past medical histories were noncontributory. The developmental history was normal except that she did not walk until 18 months of age at which time a waddling gait was noted by the parents. The dietary history was not unusual and a multivitamin had been taken since 1 month of age. The peculiar gait persisted and became more obvious whenever she ran. Occasionally, there was a complaint of vague leg pains.

She was a well-developed, fairly well-nourished child. General examination was irrelevant except for slightly enlarged tonsils, a small umbilical hernia, and flatfeet. Patellar and ankle reflexes were normal. The gait was of a waddle type, wide based, and without a limp. There was no clinical evidence of rickets.

Laboratory studies showed hemoglobin 10.75 Gm., erythrocyte count 3,910,000 per cubic millimeter, leucocyte count 9,000 with 31 per cent neu-

Fig. 1.—The patient stands with a typical wide base which is maintained in part during walking. Photograph taken April, 1950.

Fig. 2.—This roentgenogram shows irregular thickening and increased density of the metaphyses of femorae, tibiae, and fibulae.

Fig. 3.—Similar changes to those shown in Fig. 2 are noted in both radii and ulnae.

Fig. 4.—X-ray of skull shows thickening of basilar portion of the cranium in the middle and anterior fossae and thickening of the frontal bone.

Fig. 1.

Fig. 2.

Fig. 3.

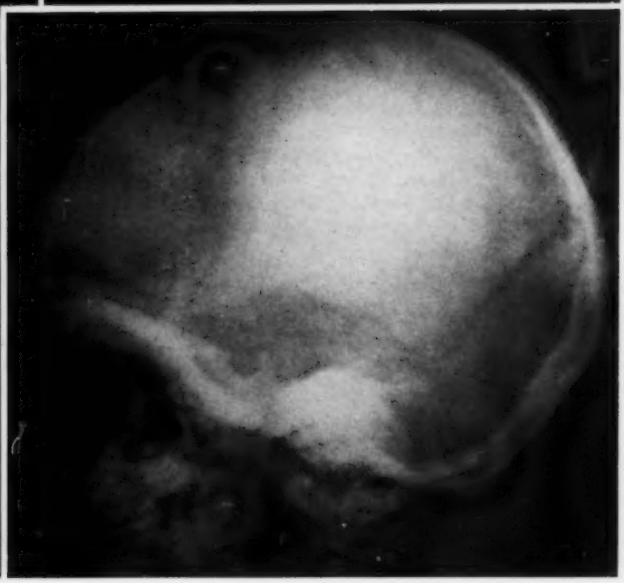

Fig. 4.

(For legend, see opposite page.)

trophiles, 60.5 per cent lymphocytes, 6 per cent eosinophiles, and 2.5 per cent basophiles. The urine, blood serology, and tuberculin skin tests were negative. Serum calcium was 10.2 mg. per cent.

The patient has been observed at frequent intervals. At the last examination on July 24, 1950, her height was 96 cm. and her weight was 12 kilograms. Complaint of leg pain was minimal. The patient appeared generally undernourished. She walked stiffly with legs apart in a straddle type of gait. (Fig. 1). She experienced no difficulty in arising from a sitting position. Moderate decrease of internal rotation of both hips was present and abduction of the left hip was increased to approximately 80 degrees. There was mild lumbar lordosis, the deep reflexes were normal, and the abdominal muscles were weak.

Roentgen studies at several visits demonstrated involvement of all long bones (Figs. 2 and 3), the skull (Fig. 4) and the clavicles. Both the roentgenologist and the authors had the impression that some involvement of the ribs was present although of insufficient degree to be conclusive. From June, 1949, to July, 1950, no significant changes had occurred in the femora. During this period, however, a slight progressive involvement of the tibiae and fibulae was evident. It was insufficient, however, to reproduce effectively in photograph.

Dr. John Caffey, who kindly reviewed the films, diagnosed the condition as progressive diaphyseal dysplasia.

DISCUSSION

The cause of progressive diaphyseal dysplasia is unknown. Although progression of the bone lesions have been observed in the pathologic studies described by Neuhauser, the disease would seem to be relatively self limited as illustrated by two reported patients, 24 and 28 years old, respectively, in whom the bone lesions were apparently unchanged over a period of several years. At this time no patients have been followed for a period adequate to allow conclusions as to the eventual outcome. The occasional neurologic abnormalities and the nutritional changes suggest that more than simple maldevelopment of bone may be involved in this dystrophy syndrome.

The differential diagnosis has been well reviewed by several authors and includes scurvy, Paget's disease, and polyostotic fibrous dysplasia.

Several other conditions are to be considered in differential diagnosis. In osteopetrosis (marble bones) the entire skeleton shows generalized, amorphous increased density which erases the roentgenologic differentiation between cortex, medulla, and epiphyseal plates.[6] During active scurvy there is bone atrophy of the epiphyses and metaphyses especially. When subperiosteal hematomas have occurred, the cortex will appear thickened during the healing stage, and residua of this cortical thickening may be seen for several years subsequently. In addition, transverse lines from epiphyseal plate fractures remain. In infantile cortical hyperostoses the osteosclerosis is distributed asymmetrically and may involve the ribs and mandible. The onset of bony changes is heralded by an acute febrile illness, these changes disappearing completely over a matter of years. Melorheostosis produces cortical thickening on one side only of the bones of a single extremity. Progressive diaphyseal dysplasia is the rarest of all these conditions.

SUMMARY

A case of progressive diaphyseal dysplasia (Engelmann's disease) is reported and the eight cases reported previously have been briefly reviewed.

This syndrome is characterized by progressive symmetrical enlargement and cortical thickening in the diaphyses of long bones. The clinical findings include muscular weakness with a waddling gait, failure to gain weight properly, and, occasionally, neurologic variations. As judged by reports in the literature, the syndrome is of rare occurrence though it is possible similar cases have been undiagnosed or unrecorded.

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INEFFECTIVENESS OF AUREOMYCIN IN PREVENTING THE PRIMARY VACCINIA REACTION

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THE effectiveness of aureomycin, the antibiotic obtained from *Streptomyces aureofaciens*, in controlling infections caused by certain rickettsia[1, 2] and large viruses[2, 3, 4, 5, 6, 7] suggested that this agent might be active against the virus of vaccinia. Should this be the case, the clinical management of eczema vaccinatum and of secondary vaccination would be improved. Since present information on the effect of aureomycin against these conditions is limited,[8] the following clinical experiment was undertaken.

CLINICAL STUDY

In order to test the effectiveness of aureomycin† against the virus of vaccinia, a group of twenty-nine previously unvaccinated white foundlings were vaccinated. Sixteen of the infants were treated concurrently with aureomycin while the remaining thirteen infants served as a control group. The infants in the treated group consisted of ten males and six females whose ages ranged from 3 to 18 months. The infants in the control group consisted of six males and seven females whose ages ranged from nine to thirteen months. The two groups of infants resided in different buildings of the foundling home and had no common attendants or nurses.

All infants were vaccinated by the multiple pressure technique on the same day with the same preparation of vaccinia virus. The vaccination reactions were measured three and seven days later. Temperature recordings were also made for each infant for five days after inoculation.

The infants in the treated group received aureomycin orally in doses of approximately 50 mg. per kilogram per day administered in divided doses at the usual feeding periods of 7 A.M., 11 A.M., 3 P.M., and 7 P.M. The first dose of aureomycin was administered approximately twenty hours after the vaccination was performed, and the drug was continued for the following five days.

With the exception of four infants in the treated group whose reactions to the initial vaccination are described in the following paragraph, the size and characteristics of the vaccination reactions in the treated and control groups were similar on the third and seventh days. No infant in either group showed any significant elevation in temperature.

One infant in the treated group had a delay in the evolution of the primary vaccinia lesion. He had no demonstrable reaction on the third day, but a small papule was noted on

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†The aureomycin used in this study was supplied by Lederle Laboratories, Inc.

SIZE OF PRIMARY VACCINIA LESIONS IN AUREOMYCIN-TREATED AND CONTROL GROUPS

GROUP	TREATED	CONTROL
Number in group	16	13
Size of lesions on third day		
Smallest	0 × 0 mm.*	2 × 2 mm.
Largest	5 × 10 mm.*	5 × 10 mm.
Average	3.7 × 5.1 mm.*	4.0 × 5.3 mm.
Size of lesions on seventh day		
Smallest	3 × 3 mm.	7 × 7 mm.
Largest	10 × 12 mm.	15 × 15 mm.
Average	7.0 × 8.2 mm.	8.8 × 9.4 mm.
Number achieving typical "take"	16	13

*The lesions of the three revaccinated infants were not measured on the third day.

the seventh day, which subsequently went through the usual changes characteristic of a primary vaccinia reaction, a delayed but otherwise typical "take" being obtained. Three infants showed no reaction at the site of inoculation on either the third or seventh day following administration of the virus. They were, therefore, reinoculated at a different site on the seventh day, and aureomycin was again administered according to the program previously followed. On the seventh day typical vaccinia reactions were noted which subsequently went through the usual evolution of a primary response to the virus. It would seem probable that the initial inoculation was unsuccessful because of some fault in technique.

It should be noted that every patient in each group ultimately showed a typical primary vaccinia reaction.

The data are summarized in the accompanying table.

DISCUSSION

These observations do not indicate that aureomycin alters the response of infants to the primary inoculation of vaccinia. As noted in the table, there was no significant difference in the average size of the vaccinia lesions on the third day after inoculation. The slightly smaller reactions noted in the treated group on the seventh day are probably insignificant, but might reflect a lesser degree of secondary infection with pyogenic bacteria in the treated group.

On the basis of these data it would seem unlikely that the administration of aureomycin to patients with disseminated vaccinia or secondary vaccinia would alter the course of the viral infection except as it might influence other superimposed infection.

SUMMARY

The evolution of the primary vaccinia reaction is not affected by the concurrent administration of aureomycin in doses of approximately 50 mg. per kilogram per day for a period of five days.

This study was made possible through the cooperation of St. Vincent's Hospital for Women and Children, Philadelphia, Pa.

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THYMECTOMY AND ACTH IN LYMPHATIC LEUCEMIA

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THE adrenocorticotropic hormone (ACTH) has been used by a number of investigators[1-7] in the treatment of leucemia with varying results. Dameshek and associates[1] found ACTH of no benefit in two cases of myelocytic leucemia and noted temporary beneficial results in six cases of acute and subacute lymphatic leucemia. Pearson and co-workers[2] demonstrated a reduction in size of the lymph nodes and spleens in eleven cases with varying types of lymphatic leucemia and lymphomas treated with ACTH. Pearson and associates[3] treated three children and two adults with acute leucemia with remissions in all five. Their patients relapsed in from one day to five weeks after stopping ACTH, and they concluded that the remissions were both incomplete and temporary. Spiers and co-workers[4] treated four patients with clinical improvement in three, and noted that the bone marrow did not return to normal. Farber and collaborators[5] treated one patient with lymphatic leucemia with favorable results, and Donahue and associates[6] treated one patient with eosinophilic leucemia with clinical and hematological temporary remissions. Schulman[7] noted striking temporary remissions in six of twelve children with lymphatic leucemia treated with ACTH and cortisone.

Thymectomy was performed on four previously untreated cases of lymphatic leucemia following the recommendations of Simmons[8] and the experimental work of McEndy and associates.[9] Prior to operation each patient received multiple transfusions and penicillin. These patients, reported elsewhere,[10] were later treated with ACTH in 12.5 mg. doses every six hours for two weeks and then the doses were reduced to 10 mg. every six hours for another two to six days. The cases were followed with daily blood counts and interval bone marrow studies (Tables I and II). All counts are not shown as this would be too repetitious and space consuming.

CASE REPORTS

Case 1.—P. B., white male aged 4 years, was diagnosed as lymphatic leucemia in October, 1949. Splenomegaly, hepatomgaly, generalized lymphadenopathy, intermittent fever and anorexia were present. Blood and bone marrow studies confirmed the diagnosis. From October, 1949, to April, 1950, he was repeatedly hospitalized for infections and anemia which were controlled by antibiotics and multiple transfusions. On April 27, a thymectomy was performed and the patient had an uneventful convalescence. The weight of the removed thymus

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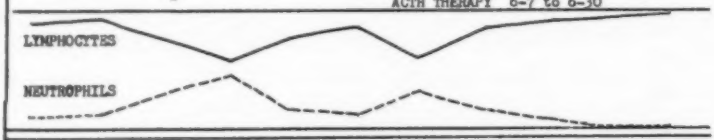
TABLE I. BLOOD COUNTS.

CASE 1. P. B.	3-10	4-25	4-27	5-3	5-10	6-6	6-12	6-16	7-5	7-21	8-24
Hb. Gms./	11	12.5		11	11	13.5	14	11	13	8	4
RBC x 10^6	4.2	4.5		3.3	4.1	4.2	3.1	3.7	4.7	3.3	1.4
WBC x 10^3	8.1	5.		5.2	3.3	3.9	3.1	3.7	3.6	3.5	1.1
PLATELETS x 10^4	22			13.			4.		1.	10.	38.

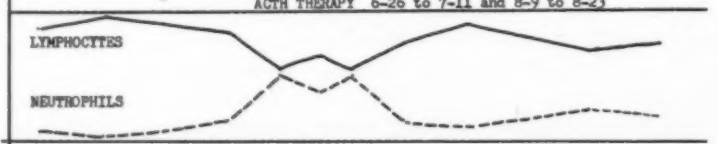
* ACTH THERAPY 6-7 to 6-30



CASE 2. I.N.J.	4-28	5-5	5-8	5-15	6-1	6-12	6-21	6-30	7-12	8-8	8-15
Hb. Gms./	9.5	16	9	12		7.5	5	125	11	7.5	
RBC x 10^6	3.6	5.2	3.5	4.2	4.7	2.9	1.6	4.4	3.8	2.2	
WBC x 10^3	6.	3.5	2.2		7.8	3	2.8	4.4		24.5	
PLATELETS x 10^4	.5	*	1			ACTH THERAPY 6-7 to 6-26					EXPIRED

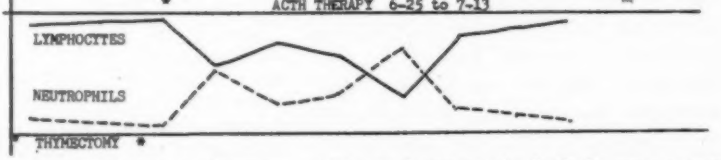
CASE 3. J.M.	5-10	5-29	6-8	6-12	6-16	6-30	7-14	8-8	8-12	8-17	8-24
Hb. Gms.	3	15		13	12	11	11.5	12	12	10.5	12.5
RBC x 10^6	.9	4.9		4.4	4.0	3.8	4.1	4.0	4.2	3.8	4.4
WBC x 10^3	3.4	1.3	2.5	2.4	2.1	2.9	6.1	1.4	1.5	1.4	4.5
Platelets x 10^4			1.			8.7	12				4.

* ACTH THERAPY 6-26 to 7-11 and 8-9 to 8-23



CASE 4. L.J.	5-28	6-2	6-8	6-17	6-19	6-26	6-30	7-10	7-14	8-3	8-7
Hb. Gms.	7.5	14	18	9.5	14	13	13.5	13	13	7	
RBC x 10^6	2.4	4.2	6.1	3.5	5.0	4.5	5.4	5.5	4.7	60.	
WBC x 10^3	72.4	13.5	9.7	1.9	2.4	2.9	5.2	5.7	6.1		
PLATELETS x 10^4				8.				1.2	1.4		EXPIRED

* ACTH THERAPY 6-25 to 7-13

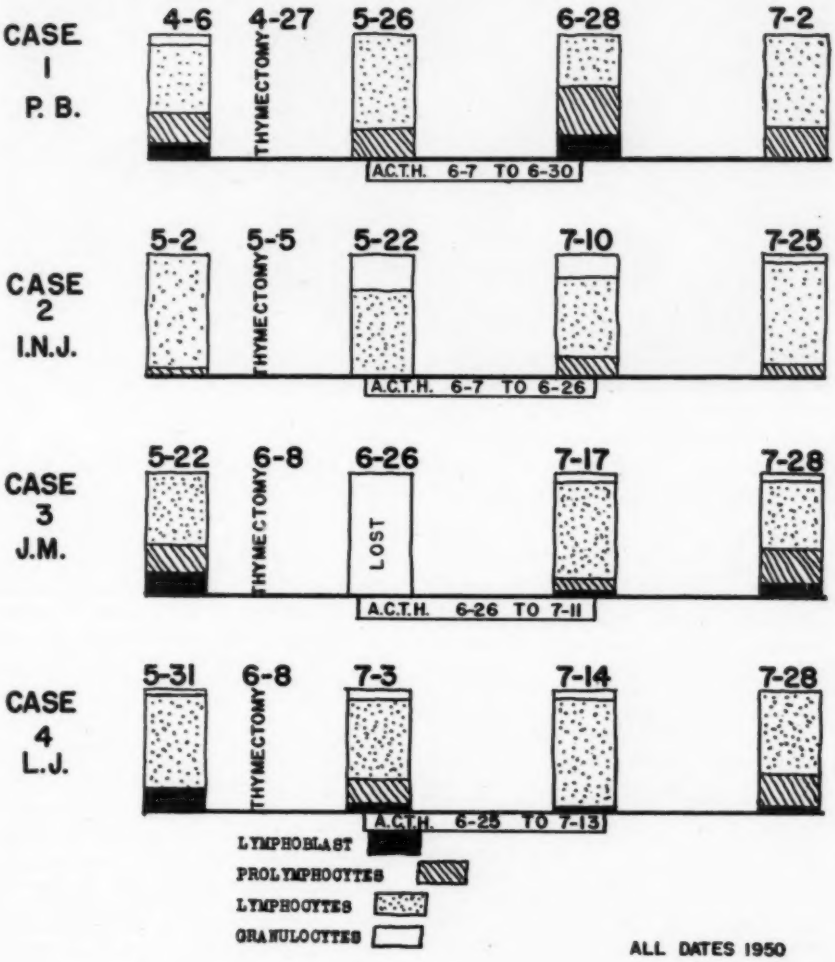


was 19 grams. Following thymectomy, there was immediate temporary clinical and hematological improvement. The clinical improvement persisted but hematologically the patient relapsed after ten days. ACTH was started forty-one days after thymectomy and continued intermittently for twenty-four days—in all twenty days. There was again clinical and hematological improvement but hematologically the patient relapsed while on therapy. The patient was discharged unimproved and is now being treated by transfusions and aureomycin.*

CASE 2.—I. N. J., white female aged 1½ years, developed postauricular

*Patient died Sept. 8, 1950, 135 days after thymectomy.

TABLE II. BONE MARROW.



swelling, hepatomegaly, anorexia, and purpuric rash with some melena, and became fretful and irritable about three weeks prior to hospitalization. The clinical diagnosis of lymphatic leucemia was confirmed by blood and bone marrow studies and a thymectomy was performed May 5, 1950, one week after admission. The weight of the removed thymus was 3.5 grams. The postoperative course was uneventful, and there was marked clinical and hematological improvement which lasted until after ACTH was begun, thirty-three days following thymectomy. ACTH therapy was continued for twenty days and the patient was discharged home still in remission. Clinical and hematological relapse occurred three weeks after stopping ACTH. She returned to the hospital at intervals for transfusions and ex-

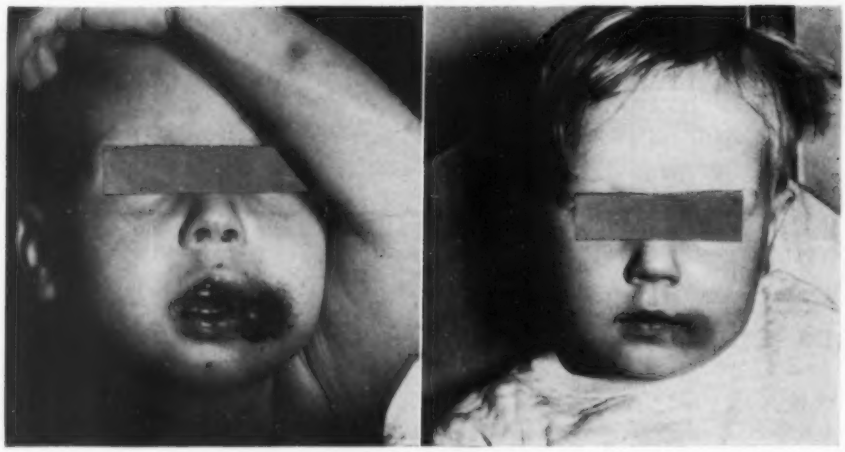


Fig. 1.—Case 3, J. M. Thymectomy performed June 8, 1950.

pired at home 102 days after thymectomy and fifty days after stopping ACTH.

CASE 3.—J. M., white male aged 2 years, became ill about eight weeks prior to admission with a generalized lymphadenopathy, splenomegaly, hepatomegaly, pallor, anorexia, and a large noma of the left cheek. The diagnosis of lymphatic leucemia was confirmed by blood and bone marrow studies. The noma failed to heal with multiple transfusions, penicillin, and aureomycin. A thymectomy was performed June 8, 1950, twenty-one days after admission to the hospital. The weight of the removed thymus was 6 grams. The postoperative course was uneventful and the noma healed rapidly (Fig. 1). There was both clinical and hematological improvement with striking improvement in appetite, activity, and general well-being. The spleen, liver, and lymph nodes became smaller, and the purpuric manifestations disappeared. ACTH was started while still in clinical remission and was continued for sixteen days after which time the patient was discharged. On returning to the hospital two weeks later, the patient had relapsed both clinically and hematologically at which time he was transfused. Thirty-eight days after stopping ACTH he was readmitted in critical condition and was given another course of ACTH, 10 mg. every six hours for fourteen days. There was dramatic improvement with a cessation of melena, disappearance of the purpura, and a return of appetite, activity, and well-being. At the time of this writing (Sept. 5, 1950) he was at home in temporary clinical remission.*

CASE 4.—L. J., white female aged 3 years, first became ill in January, 1950, with intermittent fever, progressive fatigue, pallor, anorexia, and purpuric rash. At the time of admission to the hospital (May 31, 1950), she had an enlarged spleen, liver, and a general lymphadenopathy. Hematological and bone marrow studies confirmed the diagnosis of lymphatic leucemia. After transfusions, a thymectomy was performed (June 8), and the postoperative course was complicated by shock and hemothorax. The weight of the removed thymus was 18 grams. There was both a clinical and hematological response, and seventeen days after the thymectomy, ACTH was started and continued for sixteen days. The pa-

*Patient is in clinical remission following a third course of ACTH Dec. 12, 1950, but is in hematological relapse.

tient was discharged home clinically improved but in hematological relapse. Fifteen days after stopping ACTH, she was readmitted with anorexia, generalized purpura, melena, and enlargement of spleen, liver, and lymph nodes. No funds were available for ACTH and the patient died seven days after readmission (July 1, 1950).

DISCUSSION

After each thymectomy there was a temporary left shift in the peripheral blood with an increase of leucocytes and a fall in lymphocytes (Table I). There was also a decrease or disappearance of lymphoblasts in the bone marrow in Cases 1 and 4 and a decrease of prolymphocytes in Case 2. The slide was lost in Case 3. The platelets rose in all cases except case 1 but did not remain elevated. The hematological response can probably be explained by the alarm reaction of Seyle.[11] Clinically, there was striking improvement in appetite, activity, and general well-being, which was not noted before thymectomy, although all patients had been prepared for operation by multiple transfusion. In all four patients there was a decrease in size of liver, spleen, and lymph nodes, which closely paralled the hematological responses.

The four patients received a course of ACTH therapy in from sixteen to forty-one days after thymectomy with further clinical improvement and temporary hematological improvement which lasted from ten to fifty-four days from the start of therapy. Three patients had hematological relapses while still on therapy (Cases 1, 3, and 4), and in Case 2 the remission lasted for twenty-one days after therapy was stopped. The lymphoblasts and prolymphocytes of the bone marrow increased in Cases 1 and 3 and decreased in Cases 2 and 4 following ACTH therapy.

Side effects of ACTH were infrequently encountered, although the patient in Case 4 did develop a typical "moon facies" of Cushing's syndrome. All patients received 2 Gm. of potassium chloride daily in divided doses while on ACTH therapy.

SUMMARY

1. Four patients with lymphatic leucemia were thymectomized and later treated with ACTH.

2. Temporary clinical and hematological remissions occurred following both the thymectomy and ACTH therapy.

3. All four patients relapsed. Patients 2 and 4 have died. Patient 1 has relapsed and is being treated with transfusions. Patient 3 is in temporary remission following a second course of ACTH therapy.

4. In our four cases thymectomy and ACTH were of temporary benefit in lymphatic leucemia.

5. If thymectomy is to be of any benefit, it should be performed early.

We are indebted to Dr. Carroll Shukers and Mrs. Eleanor Jackson of the Department of Clinical Pathology, University of Arkansas School of Medicine, for the bone marrow studies, and to Mrs. Carmen Downing and Miss Helen Wilson of the Arkansas Children's Home and Hospital for the peripheral blood studies.

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TOTAL ABSENCE OF THE CEREBRAL HEMISPHERES

Report of Two Cases

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TOTAL absence of the cerebral hemispheres is a very rare congenital anomaly. Two cases of this condition, both associated with arhinencephaly, were studied by us in this hospital between 1944 and 1947. Because of its rarity and because of the difficulties in differential diagnosis, it seems worth while to report them. Various names have been applied to this condition, such as "cerebral agenesis" (Riese,[1] Savatier,[2] Hutinal[3]), "aplasia of the cerebral hemispheres" (Grawitz[4]), and "hydranencephaly" (Watson,[5] following the terminology of Cruveilhier[6]). Casamajor[7] was satisfied with the title of "a child without a forebrain."

This group does not include such obvious monstrosities as cranioschisis. Also omitted from our collection of cases from the literature are those of Grawitz[4] and of Minckler and his coworkers,[8] which, although they resemble our cases in many respects, presented certain differences that seemed to justify their exclusion. Articles by Savatier[2] and by Hutinal[3] on "agénésie cérébrale" and Viana's[9] paper on "hydranencephaly" were not accessible to us.

We have accepted the following cases as probably belonging in the category with ours:

Author	*Year of Publication*	*Age of Patient*
Cruvelihier	1856	Stillborn
Hurowitz	1936	Stillborn
Licen	1921	Newborn
Ilberg	1899	6 days
Spielmeyer	1905	1 week
Spielmeyer	1905	1 week
Bettinger	1942	1 week
Watson	1944	1 week
Haler	1934	2 weeks
Watson	1944	18 days
Johnson, Warner, Simonds		20 days
Riese	1934	3 weeks
Johnson, Warner Simonds		40 days
Watson	1944	25½ mo.
Casamajor	1937	3 yr.
Edinger and Fischer	1913	3 yr. 9 mo.

Cruveilhier's case is the first record of this condition to which we had access. This was a stillborn infant. The entire mass of its brain was represented by a delicate membrane in the anterior and middle fossae of the skull and a globular mass which lay beneath the intact tentorium cerebelli. He believed that this case was one of hydrocephalus and anencephaly combined in one congenital anomaly. Hence the name "hydranencephaly," but in his earlier publication, he designated it as "cystanencephalie."

The reports of most of the cases in the literature are very brief with relatively few clinical or pathological details. As Riese[1] has pointed out, most of the authors have been more interested in the portions of the brain that were lacking than in those that were present. No detailed descriptions are

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available of the tracts and nuclei in the residual brain substance, the medulla, or the cord. Riese[1] described briefly a "precocious" and excessive myelinization in the brain stem in his case.

Total absence of the cerebral hemispheres is incompatible with life and the infants usually survive for only a short time. Cruveilhier's[6] and Hurowitz's[10] cases were stillborn, the latter being delivered by craniocelysis. Licen's[11] case was a "newborn." Ilberg's[12] patient was a 6-day-old infant whose cerebrum was absent anterior to the corpus callosum, the mammillary bodies, the fornix, and the pineal gland. Spielmeyer[13] reported two cases of this abnormality in nonidentical twins that survived for about a week. Bettinger's[14] and one of Watson's[5] patients lived 1 week each; Haler's[15] for 2 weeks; and another of Watson's[5] for 18 days. The infant described by Riese[1] lived for three weeks. In an addendum to his paper Watson[5] mentions an infant with this condition that survived for 25½ months. Casamajor's[7] patient lived for 3 years and that of Edinger and Fischer,[16] for 3 years, 9 months. Both the latter children developed marked muscular rigidity that had some of the characteristics of decerebrate rigidity. In our two cases the infants lived for 20 and 40 days, respectively.

Among the sixteen cases tabulated and summarized above, two were stillborn, eleven died within 1 month, and three survived for 25½ months to 3 years, 9 months. In nine of the eleven cases in which death occurred in less than one month and in which clinical data were available, the behavior of the infants was essentially normal for the age. Ford[17] quotes Langworthy to the effect that, "The reflex activity of the newborn human infant could all be mediated by reflexes involving the brain stem and spinal elements which have already acquired their myelin sheaths. Indeed, many pathways at birth are well medullated as high as the upper end of the midbrain, and the behavior of the newborn infant is essentially that of a brain stem preparation." According to Ford,[17] a number of reactions are elicited under normal conditions during only the first few months of life; that is, when the lack of myelination prevents cerebral inhibitions. Many of these are characteristic of decerebrate preparations.

The heads of all the above patients were approximately of normal size, except that of Cruveilhier,[6] in which the head was small, and of Hurowitz,[10] in which the head was so large that delivery required craniocelysis. The cerebral hemispheres were totally absent except possibly in the case of Riese.[1] The midbrain was defective. In most of the cases the cerebellum and pons were normal, except that in one of our patients the cerebellum was malformed. Several authors mentioned arhinencephaly which was present in both of our cases.

CASE REPORTS

CASE 1.—This white male infant, born Jan. 21, 1944, by breech delivery, was admitted to Children's Memorial Hospital in a moribund state with slow, shallow respirations and a history of slow gain in weight.

Physical examination revealed a 20-day-old, small, flaccid white male infant with a moderately large egg-shaped head and an icteric tint to the skin. The head circumference was 14½ inches; the fontanels were widely open and the suture lines separated.

The cornea of the left eye was opaque and the left pupil was pin point in size and fixed. Lateral nystagmus was observed and the reflexes were hypoactive. Diagnostic impressions were: (1) mild hydrocephalus; (2) bilateral intrauterine corneal ulceration with secondary iridocyclitis.

Treatment consisted of Coramine and adrenal cortical extract in addition to the usual routine orders.

Course in the Hospital.—The temperature remained subnormal. In the first twenty-four hours, the patient had fourteen bowel movements, did not cry, but was noted to have a sucking reflex and swallowed. The baby remained in a moribund state, became apneic on the second hospital day, and died despite stimulants.

Summary of Pathology.—The important findings were limited to the brain, and these will be described in detail. Other pathologic changes were early bilateral bronchopneumonia, hypoplasia of the adrenals, congestion of the lungs, liver, spleen, and kidneys.

The head appeared moderately enlarged and measured 36 cm. in circumference. Both fontanels were widely patent and the anterior one 8 cm. across. The lambdoidal and sagittal sutures were separated, the former by a space of about 8 mm. The scalp was retracted in the usual manner. The calvarium was opened by cutting along the suture lines. As the scissors blade penetrated the anterior fontanel, xanthochromic fluid poured from the opening. It was estimated that the cranial cavity contained 250 c.c. of similar fluid. The brain could not be palpated through the opening in the fontanel. The only evidence of a brain was a small walnut-sized structure reposing on the floor of the cranial cavity. The dura mater lined the inner table of the calvarium, and was irregular, thick, and pearly-gray with small trabeculae. The anterior,

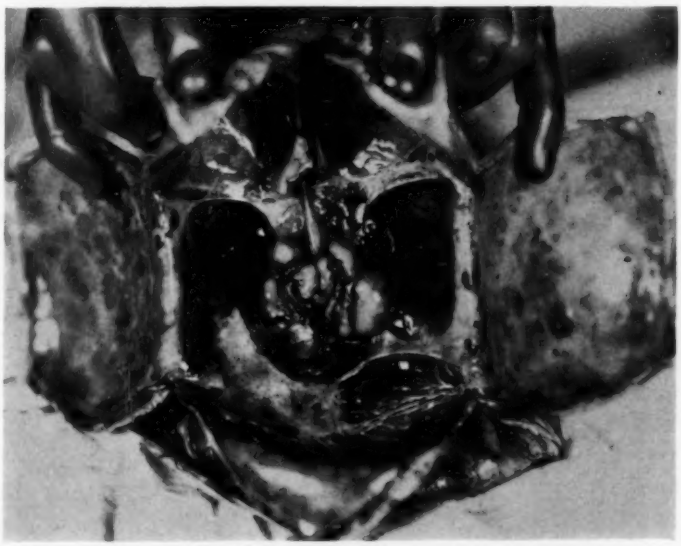
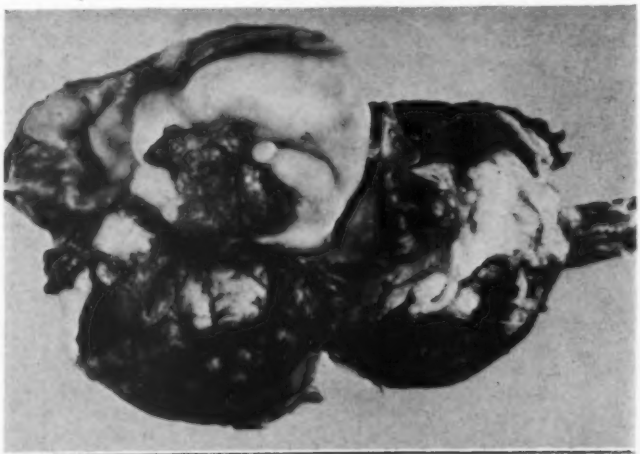


Fig. 1 (Case 1).—Base of the skull with the rudimentary brain in place. The thin membrane which lines the inner surface of the dura mater contains many small hemorrhages. The right half of the tentorium of the cerebellum is markedly fenestrated.

middle, and posterior fossae and the roofs of the orbits were well formed.

The brain tissue resembled two halves of a large walnut. Removal of the tentorium revealed a small cerebellum extending downward and posteriorly. The entire spinal cord and the mass of brain tissue on the base of the skull were removed in one piece. The weight of the entire structure was 28 grams, i.e., less than 10 per cent of the normal weight of these organs for an infant of this age (382 grams). When the "nubbin" of a brain was

Fig. 2.



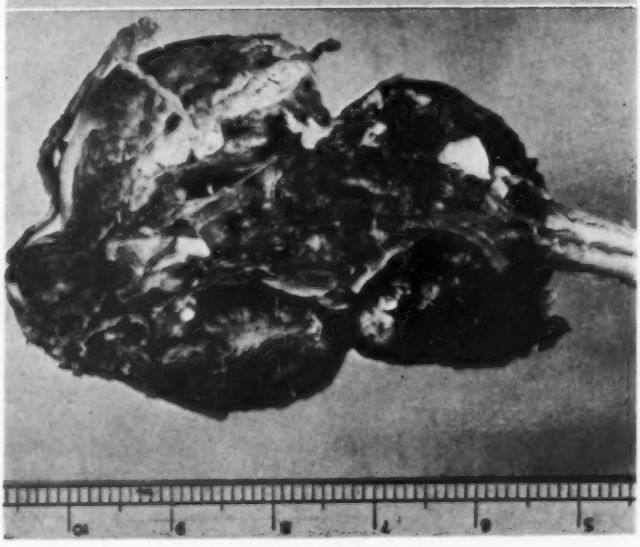


Fig. 3.

Fig. 2 (Case 1).—Upper surface of the rudimentary brain.
Fig. 3 (Case 1).—Under surface of the rudimentary brain.

removed, a tiny pair of optic nerves were seen extending from a small optic chiasm to the optic tracts.

The basilar artery and the junction with the two vertebral arteries were identified, but the internal carotid arteries were not found. Attached to the dorsal aspect of the pons was a small cerebellum represented by one small lobe, and anterior to it the lamina quadrigemina. More anteriorly, two lateral masses were identified as the thalami and the corpora striata. The left one was larger. Attached to these masses were two soft freely movable red strands, the choroid plexus. The anterior thalamic tubercles were barely recognizable. Surrounding the specimen was a torn rim of tissue identified as meninges. There was no gross abnormality of the spinal cord except that it was unusually narrow.

The olfactory nerves and the rhinencephalon were absent, but the other eleven pairs of cranial nerves could be seen extending from a fairly well-formed, small brain stem.

No microscopic sections were taken.

Diagnosis: (1) Arhinencephaly with total absence of the cerebral hemispheres; (2) partial agenesis of the cerebellum; (3) hypoplasia of the adrenals; (4) absence of the internal carotid arteries; (5) acute bilateral bronchopneumonia; (6) corneal opacity of the right eye (congenital); (7) xanthochromic pleural, pericardial, and peritoneal effusions; (8) congestion of the lungs, spleen, liver, and kidneys.

CASE 2.—This white female infant was admitted to the Children's Memorial Hospital on Nov. 29, 1947, at the age of 1 month, because of cyanotic spells with stiffness of the extremities, failure to eat and unusual downward gaze all of one day's duration. The infant was a six-week premature baby; weight at birth was 4.5 pounds. For approximately one week after birth, the baby required oxygen because of persistent cyanosis. The patient had been hospitalized elsewhere for two weeks prior to the present admission and had never cried loudly.

Physical examination revealed a small 1-month-old white female infant weighing 5 pounds, 3½ ounces, and having a moderately large head. The infant had good color. The arms and legs were spastic. The fontanels were open, large, and tense. There was separation of the suture lines of the skull. The circumference of the head was 13⅜ inches. Percussion of the skull gave a tympanitic note. The liver was palpable. The reflexes were hyperactive, and bilateral ankle clonus was demonstrated. Clinical impression: (1) birth injury—subdural hematoma; (2) hydrocephalus.

Treatment consisted of gavage feedings and daily subdural taps. On admission a spinal tap was done: pressure normal; Pandy test 3 plus; spinal fluid was clear, and cell count 7. A subdural tap was done on admission and 25 c.c. of xanthochromic fluid were removed; 15 c.c. from the left angle of the anterior fontanel, and 10 c.c. from the right. Following the subdural taps, the condition seemed to improve temporarily; the respirations were slightly deeper and the heart rate increased toward normal. Breathing again became shallow and the patient was placed in oxygen. Examination revealed depressed breath sounds throughout the entire chest with associated râles. Several subdural taps were done and approximately 15 c.c. were removed at each time. On examination of the fundi no retinal hemorrhages were seen.

Because of the yellow subdural fluid, a diagnosis of toxoplasmosis was considered. Three-tenths cubic centimeter of sediment from the spinal fluid was injected intraperitoneally into each of six white mice and all remained healthy. No toxoplasma organisms were found in the sediment from the spinal fluid. The patient became moribund and expired on the seventh hospital day.

Summary of Pathology.—The important pathologic findings in this case were limited to the brain which will

be described in detail. Other pathologic changes include confluent bronchopneumonia which was probably the immediate cause of death, hypoplasia of the adrenals, passive congestion of the liver and spleen, accessory spleen and follicular cysts of the ovaries.

The head was normal in shape and measured 32.5 cm. in circumference. The anterior fontanel was 4 cm. in its greatest diameter, was slightly bulging and tense, but the cranial sutures were not widened. The small veins of the scalp were prominent. In the skin over the anterior fontanel was an area of purplish discoloration 4 cm. in diameter and several needle puncture marks. The vertex of the skull was exposed by the usual mastoid-to-mastoid incision through the scalp. In the scalp beneath the purplish area previously mentioned there was a dark red hemorrhage into the tissues. The skull was opened by cutting along the various sutures and the bony plates were pressed outward. Upon puncturing the membrane composing the coronal suture, reddish-brown fluid escaped. The skull cavity was filled with an estimated 300 c.c. of this fluid. The only evidence of the presence of a brain was two elongated masses lying on the base of the skull and measuring about $1.5 \times 2 \times 3.5$ cm. on the left side and $1 \times 1.5 \times 2.5$ cm. on the right side. Covering and loosely attached to the inner surface of the dura mater over the vault, sides, and base of the skull was a thin grayish-red membrane which had been cut into segments on separating the bones of the skull along the suture lines. This membrane was carefully separated from the inner surface of the skull and was removed with the remnant of brain to be described later. It ranged from the thinness of tissue paper up to barely 1 mm. in thickness. Its internal surface was smooth. The falx cerebri and the tentorium cerebelli were present and in their normal locations. The internal carotid arteries were smaller than normal but could be identified. The small remnant of brain and the membrane were removed by incising the tentorium cerebelli and cutting through the spinal cord well below the medulla oblongata.

The above-mentioned membrane, the brain substance above the tentorium, the pons, cerebellum, medulla, and a portion of the spinal cord, all removed in one piece, together weighed 46 grams, approximately 11 per cent of the normal weight of the brain of an infant of this age (422 grams). Upon examining the inferior surface of this specimen, the olfactory nerves and their tracts could not be found. The remaining cranial nerves from the second to the twelfth, inclusive, were all identified (Dr. Magoun, of the Department of Neurology of Northwestern University Medical School). The optic nerves appeared to be smaller than normal and measured barely 1 mm. in diameter. The vertebral and basilar arteries and vessels forming the circle of Willis were present but much smaller than normal. The choroid plexus was easily identified and, although somewhat reduced in size, was normal in appearance.

The mass which lay above the tentorium of the cerebellum was a bilobed structure with the left portion larger than the right. The mass on the left measured $1.5 \times 2 \times 3.5$ cm.; its anterior end was rounded; it was pinkish-white in color; fairly firm in consistency; and had roughly the shape of the basal ganglia. The mass on the right was shorter and its anterior end was irregular and showed several dimples. In this mass above the tentorium the following structures were identified (by Dr. Magoun): the thalamus, hypothalamus, mammillary bodies, and small cerebral peduncles. The pons and cerebellum were present, normal in shape, but smaller than normal. The pons measured 10×12 mm., the cerebellum $2 \times 3.5 \times 5$ cm. Above and anterior to the cerebellum and on the dorsal surface, the tectum of the midbrain, the roof of the third ventricle, and one colliculus on each side were identified. In the pia-arachnoid and in the substance of the cerebellum there were numerous bright red areas

Fig. 4.

Fig. 5.

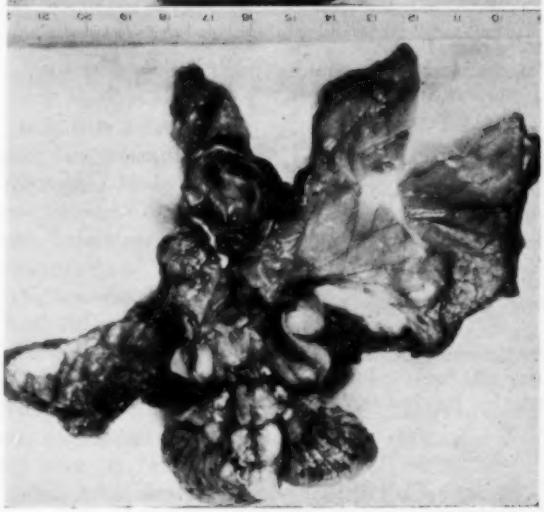


Fig. 4 (Case 2).—Upper surface of the rudimentary brain. The thin membrane which lined the inner surface of the dura mater radiates outward from the mass of brain substance.

Fig. 5 (Case 2).—Under surface of the rudimentary brain. The distribution of blood vessels in the membrane suggests those of the pia-arachnoid. The prominent olivary bodies are distinctly visible. The small optic chiasm is seen near the center of the specimen.

up to 5 mm. in diameter. On the anterior surface of the medulla there was no evidence of the pyramidal tracts, and the olivary bodies projected prominently.

Microscopic Examination.—A section of the membrane stripped from the inner surface of the dura mater showed a fine weblike structure in which were several blood vessels. Along a portion of its deeper surface was a thin layer of tissue about 50 to 60 microns thick composed of small round nuclei widely separated by a fine fibrillar material but no ganglion cells. A section from the left or larger mass above the tentorium was composed of glial tissue with a very few ganglion cells (only three found in this section). The basal ganglia were therefore very imperfectly developed. In a section of the cerebellum there was considerable recent hemorrhage both in the pia-arachnoid spaces and in the substance of the cerebellum itself. In areas not involved by the hemorrhage the cerebellum consisted of the usual three cortical layers, and the Purkinje cells appeared normal in size, shape, and number. The choroid plexus in sections was normal in structure and in appearance except that the epithelial cells covering the papillary processes contained much brown granular pigment. In a section of the upper cervical cord, the posterior columns were well developed, and the descending tracts were small. The lateral corticospinal tracts could not be identified. The gray matter of the posterior horns was relatively abundant; that of the anterior horns was normal in appearance.

Diagnosis.—Arhinencephaly with total absence of the cerebral hemispheres. Hypoplasia of the diencephalon and mesencephalon. Hypoplasia (or agenesis) of the pyramidal and corticospinal tracts of the spinal cord. Fluid-filled cranial cavity. Pigmentation of the epithelium of the choroid plexus. Multiple hemorrhages in the cerebellum. Confluent bronchopneumonia. Patent ductus arteriosus. Hypoplasia of the adrenals and kidneys. Accessory spleen. Passive congestion of the liver and spleen.

DISCUSSION

The two cases which came to autopsy in this hospital showed striking similarities. Clinically: the patients survived 20 and 40 days, respectively. There was a history of weight loss, respiratory distress, and feeding problems. Physical examination in both infants demonstrated nystagmus. The patient in Case 1 had a subnormal temperature. The patient in Case 2 showed some evidence of spasticity.

Pathologically these two infants were almost identical. The olfactory nerves and tracts (rhinencephalon, archipallium) and the cerebral hemispheres (telencephalon, neopallium) were absent; that is, portions of both lower and higher parts of the brain failed to develop.

Arhinencephaly has been reported with other anomalies of the brain. Shryock and his co-workers[18] found it associated with agenesis of the corpus callosum and with porencephaly. It has been suggested that cases such as the ones here reported are extreme grades of porencephaly. Haler,[15] who described very briefly "a specimen of a case of absence of the cerebral hemispheres, in which the infant lived two weeks" left unanswered his own question "Is this a case of extreme porencephaly?" Since porencephaly is characterized by the formation of one or more spherical cavities within the brain and since the skull cavity is not itself spherical, the coalescence of multiple cavities would not fit smoothly on the inner surface of the skull. This might, therefore, furnish an explanation for those cases, such

as Casamajor's[7] and Watson's[5] in which a small amount of brain tissue was found in the membrane which enclosed the fluid and was loosely attached to the inner surface of the dura mater.

In each of our cases there was a very thin membrane which could be separated from the inner surface of the dura mater. In our Case 2 in which this membrane was examined microscopically it apparently consisted of glial tissue but nothing resembling ganglion cells was found. These two cases were not simple hydrocephalus. Even in extreme hydrocephalus with tremendous increase in the size of the head and enormous dilatation of the lateral ventricles, there is inequality in thickness and therefore in the degree of atrophy of different parts of the cerebral hemispheres. In our cases, the membrane lining the vertex, lateral aspects, and base of the skull was nowhere more than 1 mm. thick. The same reasons will probably exclude porencephaly as the cause of the condition found in the brains of the two cases here reported. The presence of arhinencephaly in both patients and of partial agenesis of the cerebellum in one infant support the view that the lesion in our cases was on a developmental basis and was therefore a true total agenesis of the cerebral hemispheres.

Watson[5] does not agree with this explanation and presents two reasons why agenesis does not explain the absence of the cerebral hemispheres. (1) In his cases, the brain could be "reconstructed" by filling the membrane which lined the cranial cavity with cotton. (2) The fact that these infants had fairly normal appearing skulls indicates, in all probability, that the disturbance causing the disappearance of the previously formed cerebral hemispheres began rather late in fetal life, "according to Dr. Crosby, about the 5th month of fetal development." Thereafter, according to Watson,[5] the brain underwent regression. It is difficult to conceive of any type of disturbance that could cause such complete regression of previously formed cerebral hemispheres and rhinencephalon. Watson[5] quotes Ibraham who described a peculiar type of liquefactive change in brains of the newborn infant as a result of circulatory changes and anoxia. On the other hand, Altschul[19] has reported the case of a 9-month-old infant with endarteritis obliterans of the cerebral arteries and marked atrophy of the brain (16 per cent of normal weight). The cerebral hemispheres were present but small.

In both infants the arteries that supply the brain were much smaller than normal, and in Case 1 the internal carotids were not found. It would be fruitless to speculate whether the brains in these infants failed to develop because of deficient blood supply or whether the intracranial arteries did not grow because the underdeveloped brain needed relatively little nourishment.

In each of our patients the adrenals were definitely smaller than those in normal infants of corresponding age. Small adrenals are also characteristically found in cases of all types of anencephaly.[12] The diminution in the size of the adrenals was due largely to the disappearance of the wide androgenic zone which constitutes a large part of the adrenals of the newborn infant. Angevine[20] studied eighteen anencephalic monsters and found that the adrenal glands were small and of

the adult type because prenatal atrophy had occurred in the developing adrenal tissue.

The clinical and pathological differential diagnosis of cerebral agenesis involves a consideration of at least three diseases: subdural hematoma, toxoplasmosis, and hydrocephalus. During the period of hospitalization of the patient in our Case 2, all three of these conditions were considered.

1. Subdural hematoma: An infant with a subdural hematoma may exhibit many of the signs and symptoms of the cases here presented. There may or may not be a history of birth or other trauma. A baby with a subdural hematoma may be very irritable or may have convulsions; on the other hand, he may be stuporous or comatose. Breathing is often irregular, and cyanosis may be present. The reflexes may be hyperactive. Retinal hemorrhages are usually present. Bradycardia may occur. The head may be enlarged. Fluid obtained by subdural tap may range from a straw-color to reddish or red-brown, and may be obtained from one or both sides. Pneumoencephalogram shows distortion rather than destruction of the brain with or without displacement of the ventricles. Subdural and spinal taps, ophthalmic examination, and pneumoencephalograms are very important aids in the differential diagnosis of subdural hematoma.

2. Toxoplasmosis: We have studied two cases of this disease in this hospital. The diagnosis of toxoplasmosis was considered in Case 2, because xanthochromic fluid is characteristic of toxoplasmosis of the brain. Several attempts were made to find the microorganism in the spinal fluid sediment, but the tests were all negative.

The characteristic findings of toxoplasmosis are: (1) xanthochromic cerebrospinal fluid; (2) irregular areas of calcification in the brain revealed in roentgenograms; (3) chorioretinitis centralis; (4) hydrocephalus or microcephaly; (5) convulsions; (6) demonstration of the microorganisms, (a) by smears and (b) by animal inoculation of sediment from the cerebrospinal fluid. The cerebrospinal fluid shows a high cell count with a predominance of monocytes, increase in total protein, and a decrease in sugar and chlorides. If materials are available, the neutralizing antibody and complement fixation tests may be done. Since toxoplasmosis in the newborn infant is always the result of intrauterine infection, the symptoms and signs are present at birth and the infant usually dies within a few weeks or months after birth. Pneumoencephalograms reveal destruction of the brain substance.

3. Hydrocephalus: In this condition the head increases in size with wide separation of the cranial sutures and enlargement of the anterior fontanel. The veins of the scalp may be distended. Nystagmus and convergent squint may be present. An associated spina bifida or meningomyelocele are frequent associated findings. Reflexes may be exaggerated and the muscles of the extremities rigid. A tympanitic note may be heard over the distended cerebral ventricles. The child is usually mentally retarded and lethargic. A cranial tap yields crystal-clear colorless fluid. Pneumoencephalograms and the dye test may yield useful information.

4. Total cerebral agenesis: In contrast to the above three clinical and pathological entities, an infant with

total cerebral agenesis may appear quite normal for a few days or several weeks. Usually the head is not increased in size or only slightly so; the sutures may or may not be separated, and the fontanels may or may not be enlarged. A tympanitic note can be elicited over the skull. The child may be either irritable or in coma. Hyperactive reflexes and subnormal temperatures are present in some but not in all cases. One or more of the cranial nerves may be nonfunctioning. Decerebrate rigidity may be present. The intracranial fluid is xanthochromic as in toxoplasmosis, but the conclusive differential diagnostic features are (1) the absence of evidence of calcification in the brain by x-ray examination, and (2) failure to find the toxoplasma in the cerebrospinal fluid.

SUMMARY

Two cases of total absence of the cerebral hemispheres associated with arhinencephaly are reported. These infants reached the ages of 20 and 40 days, respectively. The weights of the brains were only 10 and 11 per cent of the normal for the age. The differential diagnosis of subdural hematoma, toxoplasmosis of the brain, hydrocephalus, and total cerebral agenesis is discussed.

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Case Reports

POLIOMYELITIS IN THE EARLY NEONATAL PERIOD: REPORT OF A CASE OF POSSIBLE INTRAUTERINE INFECTION

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POLIOMYELITIS occurs uncommonly before the age of 1 year, and is most unusual in infants younger than 6 months. The rarity of this disease in this group is thought to be the result of transplacental transfer of neutralizing antibody against poliomyelitis virus from the mother to the fetus, as demonstrated by Aycock and Kramer.[4] By analogy with other infections this protection has been assumed to persist for about six months. Mouton, Smillie, and Bower[15] reported poliomyelitis in ten patients less than 6 months of age, and summarized the findings in seventeen others which they collected from the world literature between 1897 and 1948. Up to 1942, sixty-three infants with this disorder were recorded in the American literature (Hess, Levenson, and Hess.[11]). Campos[7] observed at least sixty patients under the age of 5 months with this infection in Brazil; the youngest were 3 and 5 days old, respectively. Thus, the number of known instances of infantile paralysis in very young children is about one hundred fifty; were recognition of cases more thorough and reporting more complete, the total would undoubtedly be considerably greater.

Most of the attacks of poliomyelitis in infancy have occurred usually after the first two weeks of life. However, one patient is said to have been 8 days of age,[16] another 11 days,[5] and the youngest, mentioned by Aycock,[2] only 2 days old. It is striking that not many of the children had known contacts, and very few were born of mothers with acute poliomyelitis at term, in spite of the fact that hundreds of cases of early and late pregnancy complicated by this disease have been recorded;[1, 3, 8, 14, 17] almost invariably the offspring showed no evidence of infantile paralysis.

The patient described in the present report is, therefore, interesting in several respects. Born in a tank respirator of a mother dying with fulminating poliomyelitis, he developed the first signs of illness on the sixth day of life. A number of the clinical manifestations which he presented are reputed to be exceedingly rare when poliomyelitis affects young infants.

CASE REPORT

The patient's mother, a 23-year-old white housewife and mother of two other children, was admitted to the hospital with a history of an upper respiratory infection three weeks prior to the development of severe malaise, headache, and backache. These symptoms were thought to be due to incipient labor, and she was hospitalized for delivery. The following morning definite weakness of the right leg and nuchal and spinal rigidity were noted. Examination of the cerebrospinal fluid disclosed many cells, the majority of which were said to have been lymphocytes. Because of these findings she was transferred to the Haynes Memorial Hospital on June 30, 1949. On admission to this institution, the patient appeared acutely and seriously ill and was moderately dehy-

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drated. The temperature was 101.4° F. rectally, the pulse 130, respirations 28 per minute and shallow, and the blood pressure 118/72. The uterus was full-term with an active fetus in the left occiput anterior position; the fetal heart rate was 160 per minute. The neck and spine were rigid, and the Kernig and Brudzinski signs were positive. Both lower extremities exhibited flaccid paralysis of all of the major muscle groups, and there was complete areflexia. The remainder of the physical examination was within normal limits. Examination of the blood and urine revealed a moderate hypochromic anemia and evidence of dehydration. The spinal fluid was clear, under a pressure of 165 mm., and contained 3 erythrocytes and 415 white blood cells, of which 15 per cent were neutrophiles, per cubic millimeter; there were 57.5 mg. of protein and 58 mg. of sugar per 100 c.c. and 117 meq. of chlorides per liter. The colloidal gold reaction was negative.

Within three hours after admission to the hospital the patient began to develop rapidly progressive paralysis of the muscles of the chest, abdomen, and diaphragm, and became cyanotic. She was placed in an Emerson tank respirator and given oxygen. Both arms soon became markedly weak. Strong uterine contractions started in a short while, and an apparently normal male child was born without difficulty, all of the manipulations incident to delivery being carried out within the respirator. The infant was allowed to remain within the machine until the placenta was expressed (about ten minutes). The mother remained in a stuporous state, required constant mechanical respiration, and showed advancing paralysis until one week later when she suddenly became deeply cyanotic, failed to respond to the usual emergency measures, and expired. The significant findings at necropsy performed five hours after death were marked swelling and softening of the entire spinal cord and brain and basal pulmonary atelectasis. Histologic examination of the nervous system tissues confirmed the clinical diagnosis of acute poliomyelitis.

The infant cried lustily immediately after delivery and no abnormalities were found on physical examination. His weight was 6 pounds, 13.5 ounces, and the vertex-to-heel length was 20¾ inches. The temperature was 97.4° F. rectally, pulse 130 per minute, and respirations 26 to 30 per minute. He was placed in strict isolation in an electrically heated crib in a room apart from his mother. Vitamin K was administered intramuscularly shortly after birth. The low body temperature gradually rose toward a high normal level, and the child appeared to be getting along very well. On the sixth day of life, however, his complexion was grayish, pale, and sallow, and he passed several very watery stools. Loose bowel movements continued, and irritability and fretfulness followed by marked lassitude and lethargy appeared on the following day. The youngster was strikingly limp when lifted out of the crib at this time. The temperature reached 100.4° F. Within the following forty-eight hours unresponsiveness and lethargy increased. The skin was cold, and the ears, lips, and extremities cyanotic, in spite of the warmed crib and the administration of oxygen; there was no evidence of functional respiratory impairment or distress. The neck was supple but the back was stiff, and mild opisthotonus was present. The white blood count was 18,750, with 44 per cent neutrophiles. Early weakness of both lower extremities progressed rapidly to total inability to move the right leg and considerable difficulty in moving the left. The patient reacted to painful cutaneous stimulation by crying, closed his eyes in response to bright light, and blinked when a loud sound was made; there was no gross loss of sensation in the affected limbs. Lumbar puncture was attempted but only blood was obtained; a cisternal puncture per-

formed several hours later also revealed bloody cerebrospinal fluid (with xanthochromic supernatant) containing 337,000 erythrocytes and 660 white blood cells per cubic millimeter (the R.B.C./W.B.C. ratio was approximately the same as that in the blood). The supernatant fluid contained 224 mg. of protein, 71 mg. of sugar per 100 c.c., and 111 meq. of chloride per liter; the colloidal gold reaction was 0111234432. Cisternal tap repeated two days later again disclosed bloody fluid which was xanthochromic when centrifuged; there were 9,100 erythrocytes and 187 white blood cells (88 per cent lymphocytes) per cubic millimeter with an excess of leucocytes to red blood cells when compared to the blood. On this day the patient's neck as well as his back were somewhat rigid. During the next few days definite gradual improvement in all respects was apparent except for the persistent paralysis of the right leg. Physiotherapy to the affected limbs was begun, and a splint applied to the right leg, at intervals, in order to manage a developing foot drop.

No improvement in the paralysis was observed at the time of discharge from the hospital on the sixty-eighth day; the patient had gained five pounds in weight during this period. He was transferred to an orthopedic hospital for children where, during the next six months, his general condition remained excellent but no change in the degree of paralysis of the right leg was noted despite intensive physiotherapy. At the age of 1 year, the child was admitted to another hospital for surgical correction of a severe flexion-abduction deformity of the left hip with subluxation. The right leg still showed marked paralysis of all of the muscle groups, while the left one was still moderately weak.

DISCUSSION

The youngest known patient with probable poliomyelitis is the one observed by Aycock.[2] He saw a child who developed a flail leg on the second day of life; careful inquiry into the mother's history disclosed rather definite symptoms consistent with an attack of nonparalytic poliomyelitis five days before delivery. Biermann and Piszczek[5] described another early case with a history quite similar to the one reported by us. A young woman at term developed a backache which was thought to be due to the onset of labor. The day following delivery of an apparently healthy baby, she had fever, stiff neck, stiff back, "positive" spinal fluid, and muscular weakness. Cyanosis preceded death on the fourth post-partum day. The only postnatal contact of the infant with his mother was for ten minutes several hours after birth. The child appeared normal until the eleventh day of life when listlessness and slight cyanosis were observed. In the next two days definite weakness of all four extremities became apparent, and the spinal fluid was found to contain 57 leucocytes. Signs of meningeal irritation were absent; it should be noted that Mouton and co-workers,[15] in their review of the clinical manifestations in twenty-seven infants with poliomyelitis, pointed out that none had signs of meningitis or gastrointestinal disturbance. In contrast, our patient displayed both nuchal and spinal rigidity, and had severe diarrhea.

While it is generally assumed that the transmission of antibodies against the poliomyelitis virus occurs regularly in utero, transplacental infection with this agent appears to be extremely unusual. The fact that practically all pregnant patients in the acute phase of the disease give birth to perfectly normal infants who remain well supports this concept. It is conceivable, however, that in certain instances the placental barrier may break down and the embryo become infected. Although there are no definitely proved examples, Aycock's case of poliomyelitis in a 2-day-old infant[2] is most suggestive of an intrauterine infection, since incubation periods of less than six days are extremely uncommon. Our patient, with the first symptoms

appearing on the sixth day of life, is borderline in this respect. If the three cases discussed above cannot be considered as having contracted the disease in utero, two other possibilities suggest themselves. (1) Exposure during the period of delivery; the infant is in contact with maternal fecal material while being born, in spite of the best aseptic practice. (2) Exposure to contacts other than the mother; our patient, like the one of Biermann and Piszczek,[5] was carefully isolated from the mother and other patients immediately after birth. It is possible, however, that, despite rigid precautions, the child may have been exposed to one or more of the attending personnel who might have been carriers of poliomyelitis virus.

A review of the available reports[5, 6, 9, 10, 11, 12, 13, 15, 16] reveals that, although there is frequently a suggestive clinical pattern, many of the classic symptoms and signs of poliomyelitis may be absent or minimal in young infants. This probably accounts for the fact that the diagnosis of this disease is often not suspected in this group until actual weakness or paralysis appears, since anything less does not rouse sufficient suspicion to lead to examination of the spinal fluid or, in some cases, even to the child's being brought to the attention of a physician. By the time that loss of muscle function becomes established the early phase of the disease is often over and fever may be absent. About one-half of the records in the literature describe extreme "limpness" or striking total flaccidity of the body due to generalized rather than any localized weakness. In many of these babies mild or transient cyanosis, without evidence of respiratory apparatus involvement, has been described. Marked changes in behavior and alarming increase or cessation of crying with fretfulness and irritability or, as is more common, listlessness and lethargy are most striking. Diarrhea may be present in association with some of the other manifestations.

Careful search for some of the suggestive clinical manifestations in the neonatal period in infants born of mothers with acute poliomyelitis may lead to an earlier suspicion of this disease; examination of the spinal fluid, while difficult because of the frequency of "bloody taps," may establish the presence of the pre- or nonparalytic forms, in addition to proving the existence of the paralytic type. It is possible that some of the "normal" infants reported to have been born of mothers with this acute infection of the nervous system may actually have had mild, unrecognized attacks of poliomyelitis. In addition to leading to the more frequent diagnosis of infantile paralysis in very young children, such observations might also shed more light on the problem of transplacental transmission of the virus.

CONCLUSIONS

1. A case of poliomyelitis in a 6-day-old infant born of a mother who died of the disease is described.

2. The incidence of poliomyelitis in children delivered to mothers in the acute phase of the disease is very low.

3. Transplacental transmission of the virus of infantile paralysis, although possible, is not proved.

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SALMONELLA BAREILLY MENINGITIS IN A CHILD SUCCESSFULLY TREATED WITH INTRAVENOUS AUREOMYCIN

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PURULENT meningitis in infants caused by Salmonella is a rare condition. The literature on this subject has been critically reviewed by Bahrenburg and Ecker,[1] Ramon Guerra and associates,[2] Neter,[3] and most recently by Henderson.[4] Counting this and all other authentic cases, there have been less than 150 cases recorded, including an unusual explosive epidemic in Cuba of twenty-one cases in newborn infants caused by *S. havana* (Curbelo and Martinez Cruz[5]). Many cases, however, are doubtless missed because of inadequate bacteriological facilities, hence it is well to consider this type of infection in any variety of meningitis in children not readily identified as one of the commoner varieties.

The mortality rate with this infection has been extremely high. Only one of forty-nine patients less than 9 months of age recovered, whereas seventeen of eighty children in the older age group recovered.[4] Most of the patients who lived suffered from infections with *S. paratyphi A*, *S. paratyphi B*, and *S. panama*, and the majority of the fatal cases from *S. choleraesuis*, *S. enteritidis*, and *S. havana*, hence it is evident that the mortality rate depends upon the age of the patient and the strain of organism involved.

It was at one time thought that a particular type of Salmonella infection was caused by animal and human types, the so-called "Doctrine of Kiel." However, the prevalence of Salmonella infections in children, their susceptibility, varied clinical manifestations, and the small number of organisms required to initiate infection form the basis of the so-called "Doctrine of Montevideo," according to Hormaeche and co-workers,[6] Seligmann, Saphra, and Wassermann,[7] and Bornstein.[9] According to this widely accepted doctrine, all Salmonella, whether of animal or human origin, are potentially pathogenic for man and can give rise to one of four groups on a clinical basis: (1) gastroenteritis, (2) paratyphoid fever, (3) septicemia, (4) localized inflammations, the reaction of the infected person depending largely upon his age and general health. Meningitis is thus the result of a particular localization of the septic process.

S. bareilly is relatively infrequently found, having been isolated in only 1.9 per cent of a total of over 6,000 Salmonella studied by Seligmann, Saphra, and Wassermann[7, 8] and Edwards.[10, 11] The isolations from human sources have all been from feces, except one case of meningitis from which this organism was isolated. Unfortunately, no information is available regarding this case.[12] Most of the other isolates of this organism were from fowl and poultry products.

CASE REPORT

This patient, a 4-year-old girl, and her 7-year-old sister were brought to the office on March 7, 1950, because of an upper respiratory infection associated with cough, harsh breath sounds, and a few moist râles in both bases; temperature was normal. Both were given 150 mg. of aureomycin every six hours for a total of 1.8 Gm., and a cough prescription. Four days later, after initial improvement, the 4-year-old child was seen because of a sudden rise in temperature to 102° F., sore throat, exacerbation of cough, and in-

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ability to retain anything by mouth for eight hours. Physical examination revealed an acute tonsillitis and generalized harsh breath sounds; neurological findings were essentially negative. She was given 300,000 units Crysticillin. She was seen fourteen hours later because of severe frontal headache and marked listlessness. Physical findings were the same except for slight neck rigidity. She was admitted to the hospital with a temperature of 104.6° F. rectally, and a blood culture and spinal tap were done. The spinal fluid was cloudy, under slightly increased pressure, Pandy 2 plus, white blood count 8,000 per cubic millimeter with 95 per cent polymorphonuclear leucocytes, sugar 43 mg. per 100 c.c., total protein 100 mg. per 100 c.c., gold curve (Lange) 1354321000, Wassermann test negative. A few gram-negative bacilli were seen on direct smear. Blood count showed 4,540,000 red cells per cubic millimeter with 13 Gm. hemoglobin, 21,750 white blood cells with 63 per cent polymorphonuclears, 1 per cent basophiles, 22 per cent lymphocytes, and 14 per cent monocytes. Urinalysis was negative except for a faint trace of albumin.

Cultures of the spinal fluid revealed a gram-negative, motile bacillus. Acid and gas were produced in glucose, xylose, maltose, mannitol, dulcitol, rhamnose, and sorbitol. Lactose, sucrose, arabinose, salicin, and trehalose were not attacked. Hydrogen sulfide was produced, indol was not formed, gelatin was not liquefied, urea was not hydrolyzed, and no acetyl methylcarbinol was produced. The antigenic formula was VI, VII: y: 1, 5. . .*

Because the patient was unable to retain anything by mouth, she was given fluids, aureomycin, 100 mg. every six hours, and sulfadiazine intravenously, and Crysticillin and dihydrostreptomycin intramuscularly. When the organism was specifically identified as a Salmonella and subsequent sensitivity tests showed the organism to be moderately responsive in vitro to aureomycin, chloramphenicol, neomycin, and polymyxin D, the other drugs were discontinued and the dosage of intravenous aureomycin was increased to 100 mg. every four hours. The patient responded well to this therapy with a gradual drop in temperature and, by the fifth hospital day, began to take fluids by mouth. On the seventh hospital day another spinal tap was done. This fluid was clear, not under increased pressure, Pandy negative, white blood count 30, sugar 60 mg. per 100 c.c., total protein 21.5 mg. per 100 c.c., chlorides 640 mg. per 100 c.c., gold curve (Lange) 0011221000, culture and smear negative for bacteria. X-ray of the chest, taken at this time because of a persistent cough, revealed a generalized haziness in the left hemothorax compatible with a pneumonitis or a general pleural reaction.

Intravenous therapy was discontinued at this time. Aureomycin was given by mouth, 250 mg. every four hours for six days and then every six hours for three days. A mild thrombophlebitis developed at the site of intravenous injections, which gradually subsided. The child was discharged on the twenty-second hospital day, completely cured, and has shown no residual symptoms four months later, when last seen.

The patient had a blood culture on admission, three successive stool, urine, and gag cultures, which were all negative for Salmonella. Serum drawn two weeks after admission agglutinated the homologous strain of *S. bareilly* at a dilution of 1:5,120. Repeated stool cultures of the child's family were all negative. We were therefore unable to determine any apparent source of the infection.

TREATMENT

It is significant that, since the sulfonamides came into general usage about 1939, the recovery rate in Salmonella meningitis has been considerably higher than previously. Ten of nineteen patients have recovered since that time, or 52 per cent recovery. Peni-

*Identification confirmed by Dr. P. R. Edwards, U. S. Public Health Service, Communicable Disease Center, Chamblee, Ga.

cillin has been used and streptomycin in one case successfully.[13] Treatment of this extremely virulent infection is far from satisfactory. This case presented a therapeutic problem in the light of the newer antibiotics now available, with no previous trial in any condition of this sort as a guide. In vitro tests of the sensitivity of the organism to various antibiotics* showed it resistant to sulfadiazine, penicillins G and O, bacitracin, streptomycin, circulin, and penicillin and sulfadiazine combined. It was sensitive to 0.8 U. of polymyxin D, 3.12 U. of neomycin, 1.45 U. of chloramphenicol, and 1.6 U. of aureomycin.

Herrell and Heilman[14] found that aureomycin traverses the blood-brain barrier in therapeutic amounts when given orally. Dowling, Lepper, and Caldwell[15] found that the intravenous injection of 500 mg. of aureomycin gave detectable cerebrospinal fluid levels in four hours. The presence of a meningitis apparently made no difference in the concentration obtained, and the higher the serum levels attained, the higher the spinal fluid levels.[16] It was decided, therefore, that intravenous aureomycin was the drug of choice under the circumstances. Neter and associates[17] used intravenous aureomycin in one case of *Pseudomonas aeruginosa* meningitis and intravenously and intrathecally in a case of *Aerobacter aerogenes* meningitis, with recovery in both cases.

SUMMARY

A case of meningitis in a 4-year-old child caused by *S. bareilly* is reported. The source of the infection could not be determined. It is felt that the excellent response of the patient was attributable to the use of intravenous aureomycin.

*Performed through the courtesy of Dr. O. Felsenfeld, Hektoen Institute for Medical Research, Chicago.

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SICKLE-CELL DISEASE

Report of a Case With Anemia, Subarachnoid Hemorrhage and Cerebral Thrombosis

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ALTHOUGH Herrick[1] described sickle-cell anemia in 1910, it was not until 1923 that Sydenstricker and associates[2] reported the cerebral manifestations of this disease. Since then occasional accounts[3-32] of cerebral complications of sickle-cell anemia have appeared in the literature. Forty-five cases are recorded in these papers. In eleven cases, proof of a cerebral hemorrhage was found either in the cerebrospinal fluid or at autopsy. In twenty-four, cerebral thrombosis alone without hemorrhage was present. In the remaining ten, although cerebral signs were apparent, evidence for neither hemorrhage nor thrombosis was obtained.

Cerebral complications of sickle-cell anemia is infrequent after the anemia is corrected and the hemoglobin concentration stabilized. Walker and Murphy[24] and Almklov and Hansen[32] reported instances of subarachnoid hemorrhage appearing under such conditions. Thompson and collaborators[30] described a case of cerebral thrombosis also occurring without anemia.

It is the purpose of this paper to report a case of sickle-cell disease which illustrates (1) the occurrence of both subarachnoid hemorrhage and cerebral thrombosis; (2) the occurrence of these cerebral complications after the anemia was corrected and the hemoglobin concentration stabilized.

REPORT OF CASE

A Negro male child, aged 10 years, was admitted to the Kings County Hospital on Jan. 10, 1950.

The mother stated that her son had been feverish for six days; that this was associated with excessive tiredness, and with an episode of nosebleed.

On admission, the temperature was 103° F. A systolic murmur was heard at the second and third intercostal spaces along the left sternal border. The hemoglobin concentration was 4.25 Gm. The erythrocyte count was 1,480,000. With sodium bisulfite, the red cells showed 90 per cent sickling. The roentgenograms of the long bones disclosed cortical thinning, coarsened trabeculae, and widening of the medullary portions. Treatment consisted of blood transfusions given until the hemoglobin concentration reached 11 Gm.

On the tenth day of hospitalization, the child complained of sudden severe frontal headache, which was soon followed by generalized convulsions. The hemoglobin concentration at this time was 11 Gm. The spinal fluid was blood-tinged and under increased pressure. A diagnosis of subarachnoid hemorrhage complicating sickle-cell disease was made. In several days the patient became asymptomatic, and the spinal fluid became clear.

On the twenty-third day of hospitalization, the child again complained of severe frontal headache. Shortly, he became apathetic and uncooperative; his sphincter controls relaxed; and within twenty-four hours there developed a right-sided hemiplegia. The hemoglobin concentration was 11 Gm. The spinal fluid was clear, but under a pressure of 380 mm. of water. The pulse rate was 60. Examination of the fundi disclosed blurring of the discs, particularly the left. Due to the excessive and progressive increase in intracranial pres-

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sure, biparietal and bitemporal burr-holes were made, and the dura exposed. The cortex was soft and bulging at all locations. Neither subdural nor intracerebral hemorrhage was encountered. A diagnosis was made of thrombosis of a cortical branch of the left middle cerebral artery.

Examination one month later showed a residual hemiplegia with but slight improvement.

DISCUSSION

On admission, the patient was considered a case of sickle-cell anemia. This was verified by the presence of anemia and the sickling phenomenon. The anemia was corrected and the hemoglobin stabilized with blood transfusions. Two cerebral episodes followed: first, a subarachnoid hemorrhage; and, second, a cerebral thrombosis. The latter left the child with a residual hemiplegia.

Bauer[29] contends that sickle-cell anemia is a misnomer. He claims that the anemia is but one symptom of this illness, and suggests that the name "sickle-cell disease" be substituted. He reports six instances of abdominal and cerebral manifestations occurring without anemia. The experience with our patient leads us to support this concept.

SUMMARY

We have presented a case of sickle-cell disease with severe anemia which responded to blood transfusions. After the anemia was corrected and the hemoglobin concentration stabilized, the patient developed two consecutive cerebral complications; first, a subarachnoid hemorrhage and, later, a cerebral thrombosis which left the child with a residual hemiplegia.

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Medical Progress

AUREOMYCIN IN PEDIATRICS: A REVIEW

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INTRODUCTION

A MAJOR part of pediatric care is concerned with the prevention or management of microbial infections. Of the imposing array of recently described antibiotic substances, three, namely, aureomycin, chloramphenicol, and terramycin, can be selected as having outstanding clinical application. Other therapeutically active agents, such as polymyxin, are contraindicated for general use because of serious toxic effects. On the basis of present evidence, terramycin, the most recently introduced antibiotic, derived from *Streptomyces rimosus* appears to resemble aureomycin in its range of activity.[1] Chloramphenicol, derived from *Streptomyces venezuelae*, although in general having the same range of activity as aureomycin, is inferior to aureomycin in the treatment of gram-positive coccal infections and superior to aureomycin in the management of Salmonella infections including typhoid fever.[2] It is of interest that aureomycin and chloramphenicol do not possess a common chemical structure despite their surprising parallelism in activity. Rather than compare the relative advantages of one agent over another in a variety of infections this review will be limited to the reports dealing with aureomycin and will include some of the observations made at The Children's Medical Center. Particular attention will be paid to those infections encountered in childhood. It is clear that additional experience is needed to better define the limit of usefulness of this drug when given alone or in combination with other drugs with overlapping activity in the management of seriously ill patients. In brief, aureomycin exhibits the following advantages over previously available antibiotic agents:

1. It may be given orally and is effective against a wide variety of microorganisms, including many gram-positive and gram-negative bacteria both aerobic and anaerobic, the rickettsiae, certain viruses, spirochetes, and protozoa.

2. It is rapidly absorbed from the gastrointestinal tract, excreted in high concentrations in the urine, and can be given over a prolonged period of time with no known serious harmful effects.

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3. The development of resistance on the part of the infectious agent is not yet a significant problem.

The disadvantages of aureomycin are as follows:

1. The occurrence of gastrointestinal symptoms in some instances with oral preparations.

2. The lack of a suitable intramuscular preparation.

3. Instability in solution.

4. The predominantly bacteriostatic rather than bactericidal action.

5. The relatively high cost.

HISTORICAL

"Aureomycin: A Product of the Continuing Search for New Antibiotics" is the title of the introductory paper presented by Duggar, July 21, 1948, at the Conference on Aureomycin held at the New York Academy of Sciences.[3] Aureomycin is a product of the growth of *Streptomyces aureofaciens*, a soil actinomycetes, which Duggar described and characterized. Credit should go to the research groups of the Lederle Laboratories for pressing the development of aureomycin as a therapeutic agent. They tested the drug against fifty species of microorganisms, including both pathogenic and nonpathogenic bacteria, plant pathogens, fungi, and yeast. Many gram-positive and gram-negative microorganisms were inhibited under the conditions of the plate assay method. *Pseudomonas aeruginosa* and *Serratia marcescens*, as well as the majority of yeasts and fungi, were found to be resistant. The first publication[4] presented sixteen papers which covered the important aspects of aureomycin and corresponded with the date of its availability to the medical profession. The clinical appraisal of aureomycin had been made by a select group of competent investigators for approximately one year prior to its release. The literature on aureomycin is expanding rapidly and more than 1,300 medical publications already have appeared. A few of the many excellent reports in the literature are those of Finland and collaborators,[5] Long, Schoenbach, and coworkers,[6] Rose and Kneeland,[7] Woodward,[8] Rutenberg and associates,[9] and others.[10-14]

PROPERTIES

Aureomycin is a complex chemical compound exhibiting basic properties. The antibiotic was named aureomycin because of the yellow color of colonies of the parent actinomycetes and the golden color of the crystalline antibiotic. The free base is soluble in water to the extent of 0.5 to 0.6 mg. per milliliter at 25° C., slightly soluble in ethanol, insoluble in ether, and very soluble in aqueous solution above pH 8.5 with loss of antibacterial activity. It has a molecular weight of about 508 and contains carbon, hydrogen, nitrogen, oxygen, and nonionic chlorine.[15]

Aureomycin is soluble in acid as well as in alkaline solutions but is almost insoluble at pH 7.0. Four per cent solutions may be prepared as the hydrochloride at pH 2.5 or as a sodium salt in carbonate buffer at pH 8.5. At pH 7.5, the salt is stable, but at pH 8.5, 25° C., it loses 12 per cent of its activity in thirty minutes, 20 per cent in one hour, and 40 per cent in two hours.[16] Price and co-workers[17] studied the stability of aureomycin (hydrochloride) in various culture media (concentration 20 mg. per milliliter) and found that a variety of

substances such as peptone, beef extract, and phosphate buffer (pH 7.0) caused marked loss in potency, 76 per cent, 90 per cent, and 89 per cent, respectively, in twenty-four hours at 37° C. as compared with distilled water (46 per cent). Sodium thioglycollate tended to preserve the potency somewhat (50 per cent). Whitlock and collaborators[18] observed less than 15 per cent loss of aureomycin when 1 mg. in 1 ml. of serum was incubated for three hours at 37° C. They were unable to demonstrate any protein binding of aureomycin. Womack and associates[19] have shown that a heat-stable agent in egg yolk inhibits the deterioration of aureomycin activity which ordinarily occurs upon incubation at 37° C. The stability of aureomycin in solution is influenced markedly by temperature. A solution at pH 2.9, for example, has been maintained at ± 4° C. for twenty-three days with no measurable loss of potency.[20] Aureomycin is stable when prepared as a dried powder in sealed ampules or as concentrated solutions in distilled water at 4° C. and at 37° C.[21]

PHARMACOLOGY (STRESSING UNDESIRABLE REACTIONS)

Aureomycin was shown to have a low order of toxicity with few side reactions in extensive animal studies.[16, 22] Prolonged administration produced no detectable gross or microscopic changes. Mice, rats, and dogs given 100 to 200 mg. per kilogram per day orally for twelve weeks showed no evidence of chronic toxicity. The criteria were growth, general appearance, hematological observations including clotting time, liver function, blood sugar, blood pressure, and kidney function. Aureomycin exhibits no antipyretic activity in the rabbit or rat.

The oral administration of large doses (1.5 to 4 Gm. per day to adults, 0.5 to 1 Gm. per day to children) may result in frequent, bulky, and soft stools. Nausea and vomiting with abdominal discomfort may occur. Discontinuance of the drug or reduction of the dose usually results in the disappearance of these symptoms. No untoward reactions referable to the hematopoietic system have been noted, i.e., no anemia, agranulocytosis, or hemolysis. Macht and Farkas[23] reported a lengthening of the clotting time of the blood following a single oral dose of 250 or 500 mg. with no change in the prothrombin time. This observation remains unconfirmed. The administration of aureomycin to patients with acute or chronic leucemia does not exaggerate the bleeding tendencies associated with these diseases.[24] Intramuscular, subcutaneous, intrapleural, intrathecal, or intraperitoneal administration of aureomycin is not recommended because of its irritating effect. A suitable preparation for aerosol therapy is not available.[25] Intravenous administration with the early preparations (i.e., prior to April, 1949) diluted in M/6 lactate buffer exhibited no serious toxic effects. Phlebitis occurred after repeated infusions in 30 to 40 per cent of 116 patients so treated by Sanders and collaborators,[26] but was never sufficiently serious to prevent a patient from receiving several injections. In three patients, chills and fever followed the initial intravenous infusion. The experience with intravenous administration of aureomycin at this hospital has been entirely satisfactory

with the present preparation. It is of interest that gastrointestinal symptoms were not encountered when the drug was given intravenously. Brainerd and co-workers,[27] reporting clinical experience with 116 patients, noted nausea and vomiting in two of sixty-eight patients treated with intravenous aureomycin but in neither instance was the symptom certainly attributable to medication. Guaiac-positive stools were noted on several occasions in patients receiving oral aureomycin. Maculopapular, urticarial, or scarlatiniform rashes were observed in six patients, but in two, causes other than aureomycin medication may have been responsible. This report also noted the possibility of drug fever in two patients, the occurrence of "blacktongue" in two patients, the occurrence of vertigo in two patients after intravenous aureomycin, and erythema and pruritis of the perianal area in four patients. Rose and Kneeland[7] observed three instances of transitory vaginitis with a few of glossitis. They state that females are more susceptible than males to the side effects of aureomycin, such as nausea, vomiting, and a "metallic taste" in the mouth. Spink and associates[28] noted a Herxheimer-like reaction in the treatment of acute brucellosis with large initial doses of aureomycin. This reaction was evanescent, consisting of a rise in temperature and occasionally was accompanied by a shocklike picture with fall in blood pressure and tachycardia. A similar Herxheimer reaction has been noted by Rodriquez and collaborators[29] in the treatment of early syphilis with large doses of aureomycin. Parets[30] reported the occurrence of angioneurotic edema of the face and a generalized nonpruritic erythematous skin eruption on the seventh day of therapy for bronchiectasis (2 Gm. per day) in a 35-year-old male having multiple sensitivities. Whitlock and collaborators[18] observed more than 150 patients on aureomycin and the only evidence of toxicity or sensitivity noted occurred in three children whose skin apparently became hypersensitive to sunlight while on aureomycin. One 8-year-old child, who acquired a tan with some blistering and peeling of the skin for the first time when exposed to sun while on a maintenance dose of 250 mg. per day of aureomycin, has been observed by us. One would expect that with the increased purity of aureomycin fewer undesirable side reactions will occur. The new crystalline product recently released seldom produces nausea and gastrointestinal disturbances.

OTHER EFFECTS

Lépine and co-workers[31] have shown that aureomycin can retard the rate of growth and actually exert an injurious effect on proliferating normal tissue cells derived from explants of chick embryos grown in liquid media. The higher the concentration the greater the observable change, and when the tissue was subjected to a concentration of 1 mg. per milliliter, cell death was noted. The blood and tissue concentrations achieved in treating human infections correspond only to the lower ranges included in this study where minimal effects were observed; nevertheless, these experiments may have far-reaching implications. The effect on different tissues, both normal and abnormal at different

stages of growth, as well as the effect on healing and repair of tissue are problems posed by this study. No favorable clinical reports have appeared as yet on the use of aureomycin in carcinoma.

On the other hand, a very striking effect on the growth of animals was reported by Jukes and co-workers[32] who noted that the addition of 50 mg. of aureomycin per kilo of feed increased the rate of growth of hogs by as much as 50 per cent. Similar results have been obtained in chickens and turkeys.[33, 34] This effect has been observed with crude aureomycin mash and crystalline aureomycin hydrochloride as well. Other antibiotic substances produced a similar response but were less potent than aureomycin.[35]

Gyorgy and Stokes[36] were able to demonstrate the prevention of experimental hepatic necrosis in the rat by administering aureomycin (or streptomycin) with the ration. They postulated that the beneficial effect was obtained by the antibiotic suppression of intestinal bacteria, probably *Escherichia coli*, consequently resulting in the elimination of the toxic metabolites of these bacteria. These metabolites appeared to be not only injurious to the liver but to the general well-being of the animals.

The amount of aureomycin necessary to promote growth is far less than the commonly employed therapeutic dosage. At present the manner in which the growth-promoting effect is produced is unknown. Whether it is dependent entirely on antibiotic activity or on some action of aureomycin other than antibiotic is not yet established. Perhaps this effect on growth is due in part to the alteration of the intestinal bacterial flora, as well as the presence of vitamin B_{12} or other food accessory factors. This effect is reminiscent of the growth-promoting effect noted in children with pancreatic fibrosis treated with small amounts of aureomycin. All these children had *Staphylococcus aureus* in the nasopharynx and the persistence of the same bacterial flora despite marked clinical improvement suggested the possibility of some activity of aureomycin other than antibacterial effect.[37] It is well recognized, however, that in underweight infants and children with chronic infection the successful treatment of the infection with aureomycin (or other antibiotics) very frequently results in rapid weight gain. In a few underweight children who were otherwise apparently healthy the administration of aureomycin did not result in the desired gain in weight.[24]

ABSORPTION, DIFFUSION, AND EXCRETION

Aureomycin is absorbed rapidly through the gastrointestinal tract. It may appear in the urine within an hour after ingestion and attain a maximum concentration in the urine in four to eight hours. The urinary concentration of aureomycin after oral administration is high. On an oral dosage schedule of 15 mg. per kilogram per day, urine levels of 20 to 80 μg may be reached, while dosage schedules of 20 mg. per kilogram per day have resulted in levels as high as 80 to 160 μg per milliliter.[38] An interesting observation is the prolonged excretion of the drug; antibiotic activity has been detected in the urine three and four days following the last oral dose.[39] In view of the variation in bioassay meth-

ods and the difficulties encountered primarily because aureomycin solutions deteriorate rapidly at the pH and temperature most suitable to bacterial growth, the results of different investigators are difficult to correlate. As will be pointed out presently, the methods of assay are best considered as a rough approximation of effective aureomycin activity.

Most of the studies on the absorption and excretion of aureomycin have been made in adults. However, Whitlock and collaborators[18] at the Children's Hospital in Philadelphia have determined aureomycin levels in more than 150 patients ranging in age from newborn infants to adults. They found that a single dose of 11 mg. per kilogram gave blood levels at four hours ranging from 0.51 to 2.56 μg per milliliter with a mean of 1.21 μg per milliliter, and that doubling the dose gave only slightly higher levels ranging from 0.65 to 2.0 μg per milliliter with a mean of 1.48 μg per milliliter. In their series, the gastrointestinal symptoms were directly related to the size of the dose. Detectable levels were found in the cerebrospinal fluid in patients without meningeal inflammation and these levels seemed to show no correlation with serum levels. High levels were present in the urine for as long as nine hours after a single dose. When 6.6 mg. per kilogram were given intravenously to seven children, a level of from 0.4 to 4.0 μg per milliliter was attained at six hours. Caronamide 0.66 Gm. per kilogram given orally did not appreciably alter the peak level nor the rate of disappearance of intravenously administered aureomycin. Their studies suggested that aureomycin unlike penicillin and streptomycin is distributed rather uniformly throughout the body rather than being confined almost exclusively to extracellular fluid.

Brainerd and associates[40] noted significant concentrations of aureomycin in the blood within one hour after the ingestion of 1 Gm. by an adult, with maximum concentration falling between 0.6 and 2.5 μg per milliliter in two to four hours. When aureomycin was given in a continuous schedule of four or six hours, the levels of the drug tended to increase gradually. Lepper and co-workers[41] found the peak serum concentration closer to the sixth hour when 700 mg. were given per os, and noted that detectable amounts of drug were present in all patients tested at the end of twelve hours. After oral administration of 300 mg., the peak level was not as high, but aureomycin still was detectable in the serum at the end of twelve hours. An oral dose of 10 mg. per kilogram every six hours resulted in measurable amounts in the blood at all times during therapy. Randall and collaborators[42] noted therapeutic serum concentrations of aureomycin as long as twelve hours after an intravenous dose of 500 mg. and for as long as eighteen hours following 750 mg. doses A concentration of 2 to 4 μg per milliliter was considered to be a therapeutic concentration. Aureomycin is excreted at a rather constant rate by the kidneys in the absence of any impairment of renal function and there appears to be no "piling up" of the drug in the serum of patients receiving multiple doses.[12] Following the oral administration of 1 Gm., approximately 500 to 600 μg of aureomycin were present per gram of wet stool.[43] Aureomycin diffuses

readily through the placenta and into pleural fluid where its concentration may be approximately one-half that of the serum concentration.[12]

Placental transfer of aureomycin has been demonstrated by Herrell[12] and Guilbeau and associates.[44] The later investigators administered 200 mg. of aureomycin intravenously to eight women during labor and determined the infant and maternal serum levels of aureomycin at the time of delivery. They also studied the relative concentration of aureomycin in breast milk and sera of maternity patients receiving prophylactic doses of 2 Gm. per day. Aureomycin was present in all samples of breast milk tested, varying in concentrations from 12 to 50 per cent of the maternal serum levels.

Whether aureomycin diffuses into the cerebrospinal fluid following oral or intravenous administration to the extent of therapeutically effective concentrations is somewhat debatable. Harned and co-workers[16] found that following large intravenous doses in dogs a therapeutic level may be detected in the cerebrospinal fluid. Bryer and associates[22] were unable to detect aureomycin in the cerebrospinal fluid of experimentally treated animals. Herrell[12] states that aureomycin readily traverses the blood-brain barrier and diffuses into the cerebrospinal fluid. He also cautions against its introduction directly into the spinal canal. Brainerd and collaborators[40] were unable to detect aureomycin in two individuals with meningeal irritation who had received an oral dose of 1 Gm. one to three hours prior to the test. In one normal child aureomycin was not detected in the cerebrospinal fluid after ingestion of 2 Gm. over a period of twenty-four hours. Dowling and associates[45] were able to detect aureomycin in the cerebrospinal fluid in only one of seventeen patients within the first twelve hours of oral therapy whereas demonstrable concentrations were present after the patients had been on therapy for twenty-three hours or more. When an intravenous dose of 500 mg. was given to five patients and the cerebrospinal fluid tested three to four hours later, two patients had no demonstrable aureomycin, two had 0.06 μg per milliliter, and one had 0.03 μg per milliliter in the spinal fluid, whereas the blood concentration in each instance was the same, 2 μg per milliliter. In three patients with *Hemophilus influenzae* meningitis, no aureomycin could be detected in the cerebrospinal fluid by Drake and associates,[46] and a trace or none was found in four other patients treated by Chandler and Hodes.[47] In spite of these conflicting reports, favorable clinical responses in bacterial meningitis have occurred following the oral or intravenous administration of aureomycin.

DOSAGE SCHEDULE

The recommended oral dose is shown in Table I. The total amount may be divided into three or four doses per day. If vomiting occurs smaller and more frequent doses may be given. That considerable latitude in dosage is compatible with favorable clinical response may be seen from the studies of Olshaker and collaborators[48] in which no special attempt was made to calculate a precise dose of the drug on a weight basis in the treatment of infants and children with pneumonia.

TABLE I. AUREOMYCIN DOSAGE SCHEDULE

	ORALLY PER DAY (MG./KG.)			INTRAVENOUSLY (MG./KG.) EVERY 8 HOURS
	PROPHYLACTIC	MODERATELY ILL	SERIOUSLY ILL	SERIOUSLY ILL
Infants	10-25	50-75	75-100	10
Older children	5-20	25-50	50-75	5-8

It is likely that the dosage schedules recommended and those used in the past eventually will be shown to have been excessive. The recent report by Blodgett and co-workers[49] demonstrates that 1.0 to 1.5 Gm. of aureomycin per day was as effective in the treatment of primary atypical pneumonia as were the larger doses previously employed in the treatment of this disease. Long and associates[14] advised initial "priming" doses equivalent to one-sixth of the total daily dose at hourly intervals for three doses, followed by four-hourly doses in the treatment of acutely ill patients. The occurrence of the Herxheimer-like reactions[28, 29] in the treatment of acute brucellosis and syphilis with large initial doses suggests the more cautious administration of the drug at least in these diseases so that the full dosage is reached on about the third day.

Rectal administration of aureomycin in children produces inconsistent blood levels. Repeated rectal administration of the capsules may result in local irritation and the capsules or suppositories* are frequently expelled. Hence rectal administration should not be relied upon.[50] The intramuscular administration of aureomycin hydrochloride is not recommended because of the pain produced at the site of the inoculation. In the treatment of peritonitis or in moribund patients where oral therapy is impossible, intravenous administration at approximately eight- or twelve-hour intervals is recommended until the patient is able to take the drug orally. In seriously ill patients, combined oral and intravenous administration may be advisable. A limiting factor may be the development of thrombophlebitis at the site of the intravenous injection. Full dosage should be continued for one to two days beyond the time the patient is afebrile. Although there are striking changes in the intestinal bacterial flora during oral aureomycin therapy,[43, 51, 52] no untoward effects such as the development of vitamin deficiency symptoms have as yet been noted. However, the supplementary administration of oral vitamin B complex has been advised by Lederle Laboratories in patients on oral aureomycin for periods longer than seven days.

Aureomycin has proved to be a valuable prophylactic agent in this hospital in the management of a variety of conditions where infections are prone to develop, namely, in nephrosis, leucemia, and pancreatic fibrosis. An effective dose may be as little as 10 mg. per kilogram per day administered as one or two doses. Prolonged daily administration of this small dose over periods of six or more months has not resulted in any recognizable deleterious effects.

*Suppositories prepared by Lederle Laboratories and supplied to us for this purpose.

Difficulty is sometimes encountered with the oral administration of aureomycin in infants and children because of its taste, especially since the younger patients are unable to swallow a capsule. Spersoids,* a chocolate-flavored preparation containing 50 mg. of aureomycin per teaspoon, usually is taken without objection. A frequent practice is to mix the contents of a capsule with a sweet vehicle such as honey, syrup, or other food. Aluminum hydroxide gel should not be given with aureomycin as it interferes with the absorption of aureomycin and may reduce the serum concentration.[53]

ANTIBIOTIC ACTIVITY

Method of Assay.—As is the case with other antibiotics, microbial sensitivity is determined by titrating aureomycin in the presence of a standard dose of the microorganism to be tested under constant experimental conditions in artificial media, chick embryos, or other laboratory animals. The concentration, expressed as micrograms per milliliter required to inhibit growth, or in the case of experimental animals, to inhibit infection is taken as the minimal inhibiting dose.[54, 55] The paper disc technique of determining microbial sensitivity described by Bondi and collaborators[56] is simple and practical. A modification of this technique with a discussion of its clinical application has been reported by Guilbeau and co-workers.[44] The literature contains several references on the effects of variation in the composition of media, size of inoculum, time and temperature of incubation, etc., on the end point in such sensitivity titrations. It is suffice to say that because of these many variables, different techniques do not necessarily yield the same result, nor does the same technique, especially when time of incubation or composition of the medium is varied. Most laboratories which do aureomycin sensitivity determinations employ a standard technique so that their results are comparable, one with the other. The results obtained by a given technique in a given laboratory, however, are not necessarily comparable with those obtained by a different technique in the same or different laboratories.

Similarly, there are a number of methods for the microbiological assay of aureomycin in body fluids.[20, 40] The technique is essentially the simultaneous titration of a microorganism of known sensitivity (*Bacillus subtilis, Bacillus circulans, Staph. aureus,* etc.) in the presence of known concentrations of aureomycin and appropriate dilutions of the fluid to be assayed. The aureomycin content, expressed as micrograms per milliliter of body fluid is computed from a comparison of the two titrations. A diffusion plate method also has been employed.[57] Aureomycin assay is affected by the same variables affecting sensitivity determinations and is further complicated by the instability of aureomycin in alkaline solution as well as a number of as yet poorly understood factors such as the antagonistic effect of serum or blood.[58] Microbiological assay techniques are subject to the same limits of accuracy and reproducibility as sensitivity determinations. Two physicochemical methods for the assay of aureomycin have been described.[59]

Range of Activity.—Aureomycin, in contrast to former antibiotics, has a

*Lederle Laboratories.

TABLE II. COMPARATIVE IN VITRO AUREOMYCIN SENSITIVITY OF GRAM-POSITIVE AND GRAM-NEGATIVE MICROORGANISMS[60]

HIGHLY SENSITIVE (LESS THAN 0.1 μG/ML.)	MODERATELY SENSITIVE (LESS THAN 1.0 μG./ML.)	RESISTANT (MORE THAN 3.5 μG/ML.)
Staphylococcus aureus	*Escherichia coli*	*Proteus, spp.*
Streptococcus hemolyticus	*Aerobacter aerogenes*	*Pseudomonas, spp.*
Streptococcus viridans	*Salmonella typhi*	
Streptococcus faecalis	*Salmonella, spp.*	
Diplococcus pneumoniae	*Neisseria meningitidis*	
Corynebacterium diphtheriae	*Klebsiella pneumoniae*	
	Hemophilis influenzae	
	Shigella, spp.	

TABLE III. ANTIBACTERIAL ACTIVITY OF AUREOMYCIN

MICROORGANISM GRAM-POSITIVE[27, 39, 54, 61, 69]	MINIMAL INHIBITING DOSE μG/ML.
Streptococcus pyogenes	0.1 - 1.5
Streptococcus hemolyticus	0.19 - 3.12
Streptococcus faecalis	0.7 - 50.0
Streptococcus viridans	0.1 - 6.3
Streptococcus mitis	3.1 - 12.5
Streptococcus nonhemolyticus	0.1 -
Staphylococcus aureus	0.09 - 25.0
Staphylococcus citreus	0.09 -
Diplococcus pneumoniae	0.4 - 3.1
Sarcina lutea	0.09 - 0.19
Serratia marcescens	6.0 - 50.0
Bacillus subtilis	0.02 - 1.56
Bacillus megatherium	0.02 -
Bacillus anthracis	5.0 -
Mycobacterium tuberculosis	2.5 - 100.0
Corynebacterium diphtheriae	0.1 -

MICROORGANISMS CONSIDERED TO BE SENSITIVE ON THE BASIS OF IN VIVO STUDIES[10, 11, 27, 55, 79-89, 178, 189, 209]
Hemophilus ducreyi (Chancroid)
Pleuropneumonia group (Nonspecific urethritis)
Treponema pertenue (Yaws)
Treponema carateum (Pinta)
Treponema pallidum (Syphilis)
Borrelia novyi, Borrelia duttonii (Relapsing fever)
Leptospira icterohaemorrhagicae (Leptospirosis)
Spirillum minus (Rat-bite fever)
Donovania granulomatis (Granuloma inguinale)
Erysipelothrix rhusiopathiae
Pasteurella multocida

MICROORGANISM GRAM-NEGATIVE[27, 39, 54, 63-65, 70-78]	MINIMAL INHIBITING DOSE μG/ML.
Salmonella typhi	0.78 - 3.0
others	0.39 - 25.0
Shigella, spp.	0.1 - 5.0
Escherichia coli	0.6 - 100.0
Klebsiella pneumoniae	0.78 - 50.0
Proteus, spp.	1.2 - 288.0
Pseudomonas, spp.	50.0 - 250.0
Alkaligenes, spp.	0.19 - 50.0
Aerobacter aerogenes	3.1 - 100.0
Brucella abortus	0.08 - 2.0
Brucella melitensis	0.1
Brucella suis	0.25 - 0.5
Pasteurella tularense	8.0
Pfeifferella whitmori	6.3 - 12.5
Hemophilus pertussis	3.0 - 50.0
Hemophilus influenzae	0.1 - 1.0
Hemophilus parapertussis	5.0 - 10.0
Neisseria intracellularis	0.125 - 1.56
Neisseria meningitidis	1.0
Neisseria catarrhalis	3.1

ANAEROBIC SPECIES*[39, 55, 90, 91]	
Bacteroides funduliformis	12.0 - 13.0
Bacteroides melaninogenicus	
Anaerobic streptococci	
Clostridium tetanosporum	
Clostridium perfringens	

*In vivo, human mixed infections.

wide spectrum of activity. In general, the gram-positive species are inhibited by lower concentrations than are required for the gram-negative species (Table II). However, different strains of various species exhibit varying degrees of sensitivity, resulting in some overlapping between strains of the highly sensitive gram-positive species and those of the moderately sensitive gram-negative species (Table III).

The ranges of in vitro sensitivity for various bacterial species as reported in the literature are summarized in Table III. Such studies indicate the extremes of variation reported for different strains of the same species. It should be noted, however, that with a few exceptions, such as certain strains of *Streptococcus faecalis, Mycobacterium tuberculosis, E. coli, Klebsiella pneumoniae,* etc., the inhibiting doses are of relatively low order despite these variations. *Proteus, spp.* and *Pseudomonas, spp.* are almost uniformly resistant to relatively high concentrations of aureomycin.

There are few reports in the literature on the in vitro susceptibility of anaerobic bacteria to aureomycin. Those which have appeared, together with a few reports of the successful aureomycin therapy of anaerobic infections are summarized in Table III. Since the majority of anaerobic infections present a mixed flora it is not yet known whether the favorable clinical response is attributable directly to the inhibition of the anaerobe or indirectly through suppression of the aerobic symbionts.

In addition to these studies there are reports on a number of microorganisms in which in vitro sensitivities have not been determined because of the difficulty or impossibility of cultivating these agents in artificial media. The results of the in vivo therapy of experimental infections in animals or spontaneous infection in man suggest that these infectious agents are sensitive to aureomycin (Table III).

The wide spectrum of antibiotic activity exhibited by aureomycin becomes even more apparent in its antiviral (Table IV), antirickettsial (Table V), and antiprotozoal (Table VI) properties. The data summarized in these tables were derived from reports on the in vivo therapy of spon-

TABLE IV. ANTIVIRAL ACTIVITY OF AUREOMYCIN
(FAVORABLE CLINICAL RESPONSE)

Virus Etiology
Primary atypical pneumonia[10-13, 27, 92-97]
Lymphocytic choriomeningitis[98]
Psittacosis[27, 99, 100]
Eczema vaccinatum*[101]
Kaposi's varicelliform eruption*[102]
Herpes simplex*[103, 104]
Herpes stomatitis[103]
Herpes simplex corneae[105]
Herpes corneae virus[101, 102]
Herpes zoster†[103, 104, 106]
Herpes zoster ophthalmicus[27, 107]
Dendritic keratitis[105, 107, 108]
Epidemic keratoconjunctivitis[108, 109]
Lymphogranuloma venereum[27, 63, 87, 110, 111]
Inclusion conjunctivitis[105]
Trachoma[105, 112]
Verruca vulgaris[113, 114]
Unknown Etiology, Possibly Viral
Acute nonspecific pericarditis[13, 150]

*Reported improvement may be due to suppression of secondary bacterial infection.
†See text.

TABLE V. ANTIRICKETTSIAL ACTIVITY OF AUREOMYCIN[13, 27, 99, 100, 115-125]

Murine typhus (*Rickettsia typhi*)
Rickettsialpox (*Rickettsia akari*)
Scrub typhus (*Rickettsia tsutsugamushi*)
Rocky Mountain spotted fever (*Rickettsia rickettsii*)
Epidemic typhus (*Rickettsia prowazeki*)
Q fever (*Coxiella burnetii*)
Tick bite fever (*Rickettsia rickettsii var. pijperi*)

TABLE VI. ANTIPROTOZOAL ACTIVITY OF AUREOMYCIN

PROTOZOA	MINIMAL INHIBITING DOSE μG/ML.
Entamoeba histolytica[126-128]	0.2 - 0.8
Trichomonas vaginalis[129, 130]	0.6
Tetrahymena geleii[131]	10.0 - 20.0
*Toxoplasma gondii**[132]	-

*Protective effect in mice.

taneous infections in man as well as experimental infections in chick embryos, guinea pigs, mice, etc.

As regards the response of virus infections to aureomycin, many conflicting reports have appeared, and time for the accumulation of additional evidence is needed to clarify the present confusing situation. Rose[7] found that aureomycin had no effect on the viruses of vaccinia and herpes simplex in either mice or chick embryos; nevertheless, favorable clinical reports have appeared. The favorable response in certain human infections may have been due in part to the suppression of the secondary bacterial invasions frequently associated with these diseases. A similar mechanism probably accounts for the improvement noted in this hospital in some patients with ulcerative colitis and in one patient with sarcoidosis. In general, aureomycin is effective against the diseases caused by the large viruses (particle size approximately 210 to 450 mμ[152]) as in the lymphogranuloma-psittacosis group. No effect has been reported with the smaller viruses such as poliomyelitis (particle size approximately 25 mμ) and equine encephalomyelitis (50 mμ). The equivocal reports deal mostly with those diseases due to the viruses which occupy an intermediate position as regards size (influenza 115 mμ, herpes simplex 150 mμ, etc.).

On the other hand, the development of virus infections in patients receiving prophylactic aureomycin has been observed. Schoenbach[139] reported two cases of herpes zoster which developed in surgical patients during aureomycin therapy. In this hospital, chickenpox, rubella, and rubeola have appeared in children with pancreatic fibrosis or leucemia who were receiving prophylactic aureomycin therapy at the time of exposure and during the incubation periods of the respective diseases.

The effect of aureomycin on the protozoan cell (Table VI) are of interest since antiprotozoal activity is an unusual property for an antibiotic. In vivo as well as in vitro results with E. histolytica[126-128] and *T. vaginalis*[129, 130] are encouraging. The similarity of the range of concentration necessary to inhibit these protozoa to that required for bacterial inhibition suggests that the antiprotozoal effect is indirect, i.e., by inhibition of commensual or symbiotic bacteria. The presence of bacteria is not a problem with *Tetrahymena geleii*, a saprophytic, fresh-water ciliate, which can be cultivated in pure culture in artificial media. Experiments now in progress in this laboratory indicate that although as little as 1.0 μg. per milliliter of aureomycin interferes with the growth of *T. geleii*, concentrations of 10 to 20 μg per milliliter are required for complete inhibition.[131] These concentrations are considerably greater than those reported for *E. histolytica* and *T. vaginalis* (Table VI). Since *Toxoplasma gondii* has not been cultivated in vitro, precise sensitivity determinations are lacking. However, the protective ef-

fects reported by Summers[132] in experimental toxoplasmosis suggest that with further study aureomycin may prove to be of therapeutic value.

Aureomycin has been given a therapeutic trial in a number of experimental and clinical conditions which have been reported as showing an equivocal, slight, or no response (Table VII). The reason for failure in some instances is obscure. Pulmonary tuberculosis and tuberculous meningitis are refractory to therapy while scrofuloderma in a few instances has responded favorably.[24, 105, 139] Typhoid fever, melioidosis, and whooping cough have been reported to respond poorly to therapy although the respective etiologic agents are relatively sensitive to aureomycin. On the other hand, in certain clinical infections, aureomycin has been more effective than was anticipated on the basis of animal experimentation. This has been the experience with brucella infections[70] and may be the case in virus influenza. Finland and coworkers[153] obtained rapid clinical improvement in patients with proved influenza A infections treated with aureomycin. However, Wong and Cox[99] failed to demonstrate any action of aureomycin against experimental infections with influenza B virus. Equivocal results have been reported in infectious mononucleosis as well as in measles, chickenpox, and mumps. Such discrepancies among individual cases with the same diagnosis perhaps may be explained by

TABLE VII. MISCELLANEOUS EXPERIMENTAL AND CLINICAL CONDITIONS SHOWING AN EQUIVOCAL, SLIGHT, OR NO RESPONSE (AT DOSAGE LEVELS USED TO DATE)

Bacterial		
	Tuberculosis[14, 24, 64, 67, 133-135]	
	Salmonella infections*[14, 24, 37, 41, 42, 136-138]	
	Melioidosis[75]	
	Whooping cough*[14, 24, 72, 139, 140]	
Fungus		
	Coccidioidal pneumonia[27]	Streptothrix concretions (ocular)[105]
	Histoplasmosis[141, 142]	
	Moniliasis[24]	
Virus		
	Mumps*[13]	Influenza B[99]
	Chickenpox*[13, 27, 103, 143]	Canine distemper[99]
	Measles*[13, 14, 63]	Rabies[99]
	Hepatitis*[13, 36]	Newcastle disease[99]
	Poliomyelitis[14, 144]	Venezuelan equine encephalomyelitis[99]
		MEF-1 poliomyelitis virus[99]
Probable Virus Etiology		
	Infectious mononucleosis*[10, 11, 13, 14, 27, 36, 85, 145-147]	
	Pemphigus[10, 27]	
	Dermatitis herpetiformis[148]	
	Stomatitis ulceromembranosa acuta[149]	
Unknown Etiology		
	Common cold[14]	Acute leucemia[24, 27]
	Acute rheumatic fever[13]	Lymphosarcoma[24]
	Rheumatoid arthritis[133]	Chronic leucemia[24]
	Erythema multiforme[14]	Neuroblastoma[24]
	Noma[14]	Wilms' tumor[24]
	Reiter's syndrome[10]	Sarcoidosis*[24]
	Stevens-Johnson syndrome[24]	Molluscum contagiosum*[24, 105, 151]
	Acute hepatitis[13]	Ulcerative colitis*[9, 24]
	Letterer-Siwe's disease[24]	
	Hodgkin's disease[24, 27]	

*Favorable response reported by some investigators.

natural variations in the disease as well as by the presence, extensiveness, or absence of secondary bacterial infection, and the effect of aureomycin on the etiologic agents of such secondary infections. The remaining virus infections mentioned in Table VII appear to be refractory to aureomycin therapy in man, experimental animals, or both.

The uniform resistance of fungi and yeasts to aureomycin is as striking as is the susceptibility of other forms of microscopic life. Duggar[3] mentioned the resistance of most yeasts and fungi in the original paper describing aureomycin. Several strains of *Candida*, *Aspergillus*, *Rhodotorula*, and *Cryptococcus* have been examined for aureomycin sensitivity in this laboratory.[131] All strains tested have been highly resistant. The resistance of these and other fungi is apparent from their persistence in the stools of patients receiving oral aureomycin even after the normal bacterial flora of the stool has been suppressed. Fisher[154] reported that aureomycin was without effect in experimental cryptococcal infections in mice. The favorable response of human infection with *Actinomyces bovis* has been reported by McVay and associates.[155] Hager and collaborators[156] also have reported encouraging results with aureomycin in *Nocardia asteroides* infection.

Mechanism of Action.—The mechanism of action of aureomycin is primarily that of stasis; bacterio-, viro-, rickettsia-, etc., although sufficiently high concentrations and sufficiently long exposure will kill many microorganisms. The relapses occurring after short periods of therapy and the persistence of infectious agents in chick embryos even after adequate therapy suggest that the immune responses of the host play an essential part in the effectiveness of therapy. In this connection it is of interest to recall the observation of Robinson and co-workers[79] who were able to demonstrate the causative agent of granuloma inguinale (*D. granulomatis*) in the ulcerative lesion while healing was taking place under aureomycin therapy. In some instances, interference with the immune response of the host has been noted when effective therapy is given early in the course of the disease. Brainerd and associates[27] state that aureomycin may interfere with the development of complement-fixing antibodies in psittacosis. Although the significance of the appearance of cold agglutinins in primary atypical pneumonia is not understood, numerous observers[92, 157, 158] have noted a reduction in the cold agglutinin titer in patients treated with aureomycin. Although little is known concerning its exact mode of action, the spectrum of effectiveness as well as the relatively uniform susceptibility of various strains of a given species suggest that a fundamental mechanism, perhaps common to several types of unicellular metabolism, is involved. It is interesting that despite its marked effectiveness in vivo aureomycin shows no apparent viricidal or rickettsiacidal activity in vitro.[99] The effectiveness of oral or parenteral aureomycin in the treatment and prophylaxis of viral and rickettsial infections suggests that the antibiotic penetrates the host tissue cells.

Exposure to subinhibitory concentrations of aureomycin induces mor-

phologic changes in certain bacteria similar to those which appear following exposure to low concentrations of penicillin or streptomycin.[159, 160] However, fixed mutants, either morphologic or physiologic, have not been recovered following such exposure to aureomycin. Preliminary experiments in this laboratory[131] indicate that the growth of the yeastlike fungi, *Cryptococcus* and *Rhodotorula*, can be stimulated by subinhibitory concentrations of aureomycin in an otherwise synthetic medium, suggesting that in terms of the "disinfectant spectrum"[161] aureomycin activity resembles the sulfonamides, penicillin, streptomycin, etc., i.e., stimulation at low and inhibition at high concentrations.

Resistance.—The development of resistance in an initially susceptible microorganism following exposure to aureomycin appears to be less common than is the case with penicillin and streptomycin. In vitro increases in resistance have been observed with alpha streptococci,[11] *K. pneumoniae*, and *A. aerogenes*,[21] Group A and Group C streptococci[162] and *Staph. aureus*.[61] These induced increases in resistance are of relatively low order (2- to 64-fold). The sudden appearance of highly resistant mutants, such as commonly occurs with streptomycin and occasionally with penicillin, has not yet been observed with aureomycin. Indeed, Yow and Spink[70] failed to obtain aureomycin-resistant variants of brucella by the two commonly employed methods: (1) by studying large bacterial populations, or (2) by exposing the microorganisms to increasing concentrations of aureomycin.

Similarly, in vivo increases in resistance during aureomycin therapy are uncommon. In vivo increases in resistance have been observed with *Staph. aureus*[14, 62, 163, 164] and *E. coli*.[27] These in vivo increases in resistance also have been of a low order of magnitude, and with the possible exception of two strains of *Staph. aureus*[62, 164] and the reported instance of *E. coli*,[27] there is as yet little evidence to indicate that the development of such levels of resistance impairs the clinical effectiveness of aureomycin. Antibiotic dependence, as has been observed with penicillin and streptomycin, has not yet been reported with aureomycin.

The appearance of antibiotic resistance may be the result of either (or both) of two mechanisms: (1) survival and proliferation (selection) of the relatively resistant cells which may be present in any bacterial culture, and (2) genetic mutation. The relatively narrow ranges of aureomycin concentration required for the inhibition of the majority of strains of a given bacterial species suggests that with the exception of *Proteus, spp.*, *Pseudomonas, spp.*, and an occasional strain of other species, the susceptibility of the individual cells in a given population is unusually uniform. Preliminary experiments reported by Demerec[165] indicate that when aureomycin resistance does appear, the pattern of development resembles that of penicillin, i.e., resistance usually increases stepwise rather than at random, as is the case with streptomycin resistance. Such data on the mechanism of development of resistance are difficult to obtain because of the relatively low frequency of increased resistance and

the instability of aureomycin under experimental conditions.

ACUTE RESPIRATORY INFECTIONS

The etiology of acute respiratory infections is so diverse that only a versatile antibiotic would affect a large number of such infections. This appears to be the case with aureomycin. The bacterial pneumonias will be considered in the section on pneumococcal, and to a lesser extent in the sections on streptococcal and staphylococcal infections. The primary atypical or "viral" pneumonias and acute bronchiolitis will be discussed separately. The pulmonary involement encountered in patients with pancreatic fibrosis will be discussed in the section on staphylococcal infections. That aureomycin is beneficial in patients with proved influenza A infections with or without pulmonary involvement has been reported by Finland and associates.[153] Collins and collaborators[166] treated a heterogenous group of thirteen patients with pneumonias impossible to define etiologically by available laboratory techniques. In five the response to aureomycin was essentially the same as in cases of pneumococcal pneumonia. In the remaining eight patients the pneumonia appeared to be a complication of some other serious condition and the results of aureomycin therapy were equivocal.

The frequent occurrence of otitis media in childhood either alone, as a complication, or in association with a widespread respiratory infection usually presents no special therapeutic problem. The antibiotic employed is determined by the nature of the infecting microorganism. Inasmuch as a search for the causative agent is so infrequently made, and the response to penicillin so satisfactory, it is the resistant or the chronic case that is likely to come to our attention. This attitude is reflected in the report of one child with otitis media due to penicillin-resistant *Staph. aureus* who responded favorably to aureomycin.[167] Furstenberg[168] has published an excellent discussion on this subject.

BRONCHIOLITIS

Bronchiolitis is a respiratory disease peculiar to infants and young children and is characterized by the sudden appearance of dyspnea, retraction, fever, with or without wheezing respirations and cough. The patient usually has had a preceding mild respiratory infection and is often likely to be "plump." Upon physical examination the infant is acutely ill, often febrile, with rapid grunting or wheezing respirations presenting an emphysematous chest. Coarse rhonchi, high-pitched wheezing, or fine râles may be heard throughout the chest. The roentgenograms of the chest reveal a small heart, low diaphragm, and hyperaeration of the lungs, often with small areas of atelectasis. There is a marked seasonal incidence with variation in the severity of the infection from one season to the next. A few fatalities have been associated with serious epidemics. The etiology has not been established. However, there is suggestive evidence that it may be related to the same type of agent responsible for primary atypical pneumonia in older children and adults. Nasopharyngeal cultures reveal no uniform or consistent flora, and the white blood count may be normal or only moderately elevated with a pre-

dominance of lymphocytes. The cold agglutinin titer may rise, and the response to sulfadiazine, penicillin, and streptomycin is poor.

In the early months of 1949, a small but serious epidemic in Boston provided an opportunity to evaluate aureomycin in this condition. The effect was dramatic in twelve cases where the average duration of fever was twenty-four hours compared to approximately four days for the control group.[169] The time required in the croup-room and for the pulse and respiration to return to normal was considerably reduced, as was the hospital stay. However, the experience in late 1949 and early 1950 has been less impressive. Thompson and Spector[170] treated a larger group of thirty-two patients with aureomycin in the winter of 1948 and 1949 in Cleveland with less striking results but the drug appeared to be more effective than the sulfadiazine, penicillin, and streptomycin therapy used in thirty-two control cases. The aureomycin-treated patients were hospitalized a little over five days per patient, compared with an eight-day average per patient in the control series.

PRIMARY ATYPICAL PNEUMONIA

A number of etiological agents can produce the clinical picture of primary atypical pneumonia in man. This group of diseases has not been excluded (or included) by appropriate laboratory examinations, in many reports on the antibiotic therapy of pulmonary infections. Thus the evaluation of a therapeutic agent is difficult particularly when the correct diagnosis of the disease is supported only by laboratory evidence of an exclusive or negative nature. The appearance of cold agglutinins is not in itself sufficient positive evidence of the diagnosis of this disease. The clinical picture should be supported by epidemiological considerations. For the sake of emphasis the following conditions should be considered in the differential diagnosis: bacterial infections, particularly bacterial pneumonias, tuberculosis, tularemia; rickettsial infections such as Q fever; virus infections such as influenza, psittacosis, lymphocytic choriomeningitis, and finally fungus infections such as coccidiomycosis. The evaluation of therapy is further complicated by the fact that the beneficial effect of aureomycin in some of the above-mentioned diseases is well known. From the experimental approach, Eaton[171, 172] demonstrated the effectiveness of aureomycin in experimentally infected cotton rats and fertile hens' eggs with a virus isolated from patients with atypical pneumonia.

Atypical pneumonia occurs most commonly in the young adult but may be encountered in the older child and adolescent. Numerous reports describe a decided improvement with the use of aureomycin. The earliest reports are those of Kneeland and associates[93] (ten patients, two were 14 years of age or under), Schoenbach and Bryer[94] (thirteen patients, four were 19 years of age or under), and Finland and collaborators (twenty cases).[95] Harvey and collaborators[11] however, compared the results in a group of six patients who received aureomycin (average dose 13.3 Gm. given over an average period of 8½ days) with a group of nine controls who received no chemotherapy, and concluded that aureomycin failed to affect the course

of the disease in the small group of patients studied. The most recent report from Finland's group[173] noted a prompt and beneficial effect in each of forty cases. Five patients in this series were less than 19 years of age. The average total dose of aureomycin was 12.3 Gm. given over an average period of 3.6 days. Cold agglutinins were demonstrable in the serum of thirty-two of these patients in significant or increasing titer on or after the middle of the second week of the disease. Agglutinins for *Streptococcus MG* were found less often and the increase in titer was less striking than was the case with cold agglutinins. In order to overcome the objection which may be raised when conclusions are drawn concerning the clinical response in consecutive patients with a disease which is so variable, Meiklejohn and Shragg[92] studied a group of parallel patients at Fort Ord, Calif., during the winter of 1948-1949. They observed a prompt response in twenty-two patients treated with aureomycin and concluded that this agent is highly effective. In their control group of twenty patients treated with penicillin, variations in the duration of the disease were noted, with approximately one-half showing prompt recovery. Relapse occurred in three aureomycin-treated patients after the drug was stopped and in each instance prompt response was noted when the drug was resumed. Dowling and co-workers[13] reported fifteen cases of primary atypical pneumonia with a striking drop in temperature and clinical improvement in thirteen. The report by Olshaker and associates[48] is of particular interest inasmuch as it reviews the problems encountered in making a diagnosis in children and describes the response to aureomycin in nine children with atypical pneumonia. It should be kept in mind that there is a paucity of information concerning the serologic response, more specifically the cold agglutinin and *Streptococcus MG* agglutinin in the younger age groups. The effect of aureomycin therapy on the cold agglutinin titer has been referred to previously. Five of these patients fulfilled the criteria for diagnosis, including the development of cold agglutinins and *Streptococcus MG* agglutinins. Four of these patients showed a favorable response and became afebrile thirty-six hours after therapy was started. The fifth patient was a therapeutic failure. Four other children were regarded as having a probable viral pneumonia on the basis of negative nasopharyngeal cultures, the presence of leucopenia and failure to respond to penicillin and sulfadiazine. These patients responded favorably to aureomycin. Experience at the Boston Children's Hospital likewise lends support to the effectiveness of aureomycin in the treatment of so-called clinically atypical pneumonia.

PNEUMOCOCCAL INFECTIONS

The response of patients with pneumococcal infections to the sulfonamides and penicillin is so uniformly good that the introduction of possibly equally effective antibiotic agents seems hardly worth while. However, instances are encountered where a more widely "anti-infective" agent is desirable early in the course of therapy, before bacteriologic evidence is available as to the nature of the etiological agent. This consideration is

extremely important in dealing with mixed infections, or to the physician who is obliged to treat his pneumonia patient in the home where laboratory assistance is lacking. Further justification for the use of aureomycin occurred in the rare situation of a child with *Diplococcus pneumoniae*, type VI meningitis, who responded favorably to aureomycin after failure of sulfadiazine and penicillin.[174] Although in most cases penicillin is still the drug of choice, additional isolated reports of favorable response to aureomycin therapy have been recorded in the literature.[13, 41]

The response to the aureomycin treatment of sixteen infants and children with pneumococcus pneumonia was good in fourteen and fair in two.[48] Seven of the sixteen patients were afebrile in 12 hours; two in 18 hours; one each in 30, 36, 48, 60, and two at 72 hours. It is interesting that the slowest response occurred in those patients treated at first with intramuscular therapy. The dose was indeed small, averaging 11 mg. per kilogram per day, and was later replaced by much larger oral doses. In view of the general abandonment of this form of administration and the use of larger oral doses, more rapid clinical improvement is to be expected. In this small series of patients roentgenographic evidence of clearing of the chest was noted in four to eight days except for one patient in whom twelve days was required. *D. pneumoniae* was recovered from the nasopharynx in five of the sixteen patients as late as the fifth day, and the time of disappearance of the causative agent did not correlate with the over-all clinical improvement. Recovery was uneventful with no suppurative complications in these sixteen patients. The experience at this hospital with *D. pneumoniae* infections is equally encouraging.

A number of investigators have reported on the use of aureomycin in the treatment of adults with pneumococcus pneumonia. Dowling and coworkers[13] have reported on fifty patients and noted a rapid response in most instances, the temperature returning to normal within twenty-four to twenty-eight hours after starting aureomycin therapy. Gocke, Collins, and Finland[175] treated thirty-three patients with pneumococcus pneumonia and found oral or intravenous aureomycin highly effective. "The results in individual cases were quite decisive and the beneficial effects were demonstrated with great regularity in all patients." Most of the patients received less than 20 Gm. and were treated for five days or less. *D. pneumoniae* were obtained from the pretreatment blood cultures on eleven patients and in only one case after treatment was started. The disappearance of *D. pneumoniae* from the sputum during aureomycin therapy was more impressive than the results of similar studies in patients treated with sulfonamides or with penicillin.

STREPTOCOCCAL INFECTIONS

Inasmuch as penicillin and sulfonamides are effective in the treatment of streptococcal infections, the use of aureomycin may be limited at the present time to cases of mixed infections, to patients in whom allergic or other reactions to penicillin or sulfonamides may be anticipated, or in those instances where clinical failure with sulfonamides or penicillin occurs. However, as experience accumulates,

aureomycin may replace these well-tried agents in the management of certain streptococcal infections. That aureomycin is effective in eradicating the aerobic and anaerobic streptococci encountered in the obstetric patient has been reported in the excellent study of Guilbeau and collaborators.[44] Numerous reports can be found of individual cases or of small numbers of patients with hemolytic streptococcal infections who were treated successfully with aureomycin. Reference may be made to ten patients[166] and to two patients[49] with hemolytic streptococcal pneumonia, nine patients with scarlet fever, one with cellulitis and another with bacteremia,[13] and one with erysipelas.[27] The report of nine patients with chronic sinusitis due to mixed infections including hemolytic streptococci also should be mentioned.[176] In these nine patients aureomycin was given after failure of penicillin and sulfonamides. There are a number of individual case reports in which aureomycin was effective in the treatment of *Streptococcus faecalis* infections. Aside from urinary tract infections which have been reported to respond satisfactorily are the cases reported by Schoenbach[174] which included one case of meningitis due to *Str. faecalis* in an infant who responded promptly to oral and parenteral aureomycin; two patients with subacute bacterial endocarditis, one due to *Str. faecalis* which responded well and the other due to *Str. salivarius* which responded well at first and then relapsed with failure to respond; two patients with peritonitis, and two with localized postoperative peritoneal infections due to *E. coli* and *Str. faecalis* with immediate remissions of signs and symptoms. Harvey and associates[11] treated four patients with subacute bacterial endocarditis due to *Str. faecalis* in two patients, and to microaerophilic streptococci in the other two. A favorable response was noted in one patient with *Str. faecalis*, whereas evidence of infection persisted in the other three during or subsequent to the aureomycin treatment. Brainerd and associates[27] found that the fever and bacteremia of two patients with subacute bacterial endocarditis due to penicillin-resistant *Str. faecalis* disappeared during treatment with aureomycin, but recurred one and seven days, respectively, after the termination of long courses of therapy.

STAPHYLOCOCCAL INFECTIONS

Although penicillin has been effective in the treatment of many staphylococcal infections, an increasing number of therapeutic failures are reported in which sensitivity studies reveal penicillin-resistant microorganisms. The emergence of penicillin-resistant strains has been noted with increasing frequency since the introduction of this agent in 1941.[163, 177] Fortunately, most of these penicillin-resistant strains are sensitive to aureomycin. In spite of increasing evidence pointing to the failure of penicillin in many *Staph. aureus* infections, there is a certain reluctance in giving up a formerly effective, inexpensive, well-tolerated and easily administered agent. In October, 1949, Long and co-workers[178] stated that penicillin is the drug of choice in the treatment of staphylococcal infections and that aureomycin is the second choice. Nichols and Needham[62] isolated fifty strains of *Staph. aureus* from clinical material

submitted to the laboratory of the Mayo Clinic during a forty-four-day period ending Jan. 20, 1949, and determined the in vitro sensitivity of these strains to penicillin, streptomycin, and aureomycin. Thirty-four or 60 per cent required more than 1.6 Oxford units per milliliter of penicillin for inhibition and were considered to be penicillin resistant. Fourteen of these thirty-four strains also were resistant to streptomycin (25 μg per milliliter) whereas all thirty-four penicillin-resistant strains were found to be sensitive to as little as 0.78 μg aureomycin per milliliter. In fifteen patients with staphylococcal bacteremia observed during 1948, twelve strains were resistant to 1.6 Oxford units of penicillin, three of the fifteen were resistant to 25 μg of streptomycin, and all strains tested against aureomycin were inhibited by 0.78 μg. They treated six patients with staphylococcal bacteremia with aureomycin after penicillin in doses varying from 300,000 to 1,000,000 Oxford units per day was shown to be ineffective. Four of the patients had received streptomycin (2 Gm. per day), and three patients had received small amounts of sulfonamide. The response to aureomycin was most encouraging with clearing of the bacteremia in four patients. Nevertheless they did not advocate aureomycin as a routine in the treatment of staphylococcal bacteremia but felt that sensitivity studies should be instituted immediately in such cases and if penicillin resistance and aureomycin sensitivity are found the drug of choice is aureomycin. Lankford and Lacy[61] studied the range of tolerance of twenty-one strains of *Staph. aureus* to antibiotics. All strains were sensitive to aureomycin and all were inhibited within a very narrow range of concentration, while 25 per cent of the cultures were moderately resistant to penicillin. In discussing the correlation of sensitivity studies to clinical response, they point out that the culture most resistant to aureomycin was obtained from a patient with staphylococcal meningitis whose infection was uninfluenced by combined sulfonamide, penicillin, and streptomycin therapy, but responded dramatically to aureomycin. They pointed out that the probability of aureomycin tolerance developing during therapy is far less than the risk involved with streptomycin and penicillin. Further in vitro studies showed that when penicillin and aureomycin or streptomycin and aureomycin are combined, either combination was less effective than any of the three agents when used alone. Chandler, Schoenbach, and Bryer[179] treated seven infants with *Staph. aureus* infections during the summer of 1948. In five newborn infants the infection developed while in the nursery or shortly after discharge; two had breast abscesses, two had cellulitis, and one had staphylococcal pneumonia. These infants previously had shown no clinical response to penicillin and sulfadiazine. Marked clinical improvement was noted in all cases within forty-eight hours. A sixth infant (aged 17 months), who developed staphylococcal septicemia during treatment for eczema and hyperproteinemia, failed to respond to combined penicillin, streptomycin, and sulfonamide therapy but made a rapid, uneventful recovery with aureomycin. Another infant with multiple lung abscesses likewise improved with aureo-

mycin after failing to improve with combined therapy (penicillin, streptomycin, and sulfonamide).

Shwachman and associates[37] reported on the effect of aureomycin in thirty-five patients with pancreatic fibrosis (mucoviscidosis) with varying degrees of pulmonary involvement. The clinical response was good to excellent in thirty-one of the thirty-five patients. Response was characterized by disappearance or diminution of cough, improved general well-being, increased appetite, and weight gain. The discontinuance of the drug in most cases resulted in the prompt reappearance of symptoms. The minimal effective dose varied from 20 to 30 mg. per kilogram per day given in one or two doses. The in vitro sensitivity of strains of *Staph. aureus* isolated from the nasopharynx of these patients was determined for penicillin, streptomycin, and aureomycin. The majority of the strains were relatively more sensitive to aureomycin than to either of the other two antibiotics. The strains isolated from seven patients during aureomycin therapy showed an apparent increase in resistance ranging from 4- to 64-fold.[164] During the eleven-month period following the above report, further experience has been gained in the management of these same patients plus the addition of approximately sixty-five others. Four of the original group of thirty-five died, and in the three examined post mortem, the pulmonary changes were extensive.

The continued clinical improvement is impressive in the majority of these patients, although the disease is not cured and the nasopharyngeal cultures often remain positive for *Staph. aureus*. The dosage schedule has been modified so that the severely ill patient receives approximately 50 mg. per kilogram per day in two or three doses. After the subsidence of the severe or acute phase, a maintenance dose of as little as 5 or 10 mg. per kilogram given once daily may prove beneficial. Inasmuch as the early pulmonary lesions of inflammatory type may be reversible, it is important to administer aureomycin immediately after establishing the diagnosis even in the presence of minimal pulmonary signs or symptoms. The prolonged administration of oral aureomycin (twelve or more months) in the schedule previously mentioned has not resulted in recognizable complications or deficiency states as might be postulated when the bacterial flora of the gastrointestinal tract is altered. An aqueous multivitamin preparation is given to these patients in at least twice the usual daily dose. Whether the remarkable weight gain demonstrated by some of these patients is entirely due to the control of infection or to other properties of aureomycin is speculative. A small number of patients who previously had responded well to aureomycin are now responding poorly. In these instances the microorganism most commonly found in the thick, tenacious sputum, or mucus, is *Ps. aeruginosa*.

Other forms of staphylococcal pulmonary infections respond to aureomycin as pointed out by Dowling and associates,[13] Finland and collaborators,[5] and Olshaker and associates.[48] The use of aureomycin to stop an epidemic of puerperal breast infections associated with nasopharyngeal and skin infection in the newborn infant

in Winnipeg hospitals is described in an excellent report by McGuinness and Musgrove.[180] An 11-year-old boy with *Staph. albus* meningitis who resisted combined treatment with penicillin, streptomycin, and sulfadiazine for twelve days responded dramatically when given aureomycin.[181]

A number of miscellaneous cases of staphylococcal infections have been treated in this hospital, such as two patients with chronic osteomyelitis with draining sinuses who failed to respond to penicillin and sulfadiazine. One patient healed and the other patient was improved with aureomycin. A severely ill child with a septic joint from which penicillin-resistant *Staph. aureus* was isolated, responded favorably to aureomycin. One patient with a staphylococcal meningitis had a satisfactory bacteriologic response, one patient with a necrotic nasal septal lesion from which only *Staph. aureus* could be cultured showed a good response. One newborn infant with staphylococcal pyodermia responded well. The development of staphylococcal abscesses in debilitated patients and in patients with leucemia has been observed a number of times on the Tumor Therapy Service of The Children's Medical Center. As a rule, these patients respond to aureomycin even after penicillin, streptomycin, and sulfadiazine have failed. In one leucemic child the sites of penicillin injections (Crysticillin) became the foci of staphylococcal abscess which improved with aureomycin therapy. On the other hand, the prophylactic administration of 500 mg. of aureomycin daily did not prevent the development of a staphylococcal bacteremia in a child with leucemia. It is hardly necessary to state that the basic tenets of surgery still hold and that the administration of an antibiotic does not render unnecessary the free drainage of encapsulated pus or removal of necrotic tissue or foreign bodies.

PERTUSSIS

The evaluation of a therapeutic agent in the treatment of pertussis in infants is difficult because of the variable and prolonged nature of the disease, the possible influence of antibiotics on secondary invaders, and often the late stage of the disease in which patients may be brought to the hospital for treatment. The role of good nursing care in the management of these infants is not sufficiently emphasized in many of the reports dealing with this disease and this obviously has much to do with the speed of recovery and the development of complications. Furthermore, many clinicians will not pronounce a drug effective unless an immediate and dramatic result is produced after institution of therapy as is the case in a variety of infections. Conflicting reports can be found as regards the effectiveness of the many recently introduced antibiotic agents in this disease. Bell and associates[140] treated twenty patients with aureomycin and concluded that when the drug was started early the course of the disease was shortened. Chang and collaborators[182] treated twenty-two patients at the Boston City Hospital and confirmed the beneficial effects. Improvement began soon after aureomycin treatment was started and continued steadily in seventeen of the patients. The number, severity, and duration of paroxysms were significantly re-

duced in the aureomycin-treated patients as compared with a comparable group of twenty-two patients concurrently treated under the same conditions without antibiotics or antisera. The total duration of the paroxysms in the aureomycin-treated group continued for an average of 21.7 days after admission or 18 days after the first dose of aureomycin as compared to an average of 30.3 days after admission in the nontreated group. Of the twenty-two patients treated, nine were under 1 year, eight between 1 and 3 years, and five were over 3 years of age. The average duration of cough prior to admission was 8.8 days in the aureomycin-treated group or 12.5 days prior to aureomycin therapy as compared with 9.5 days in the twenty-two untreated patients. The first ten patients were treated with about 100 mg. per kilogram per day for five days. Because of inadequate bacteriological and clinical responses in three instances, subsequent patients were treated for ten days with a smaller dose of 60 mg. per kilogram given as four equal doses. In six patients, loose bowel movements and some vomiting occurred, but this was not severe enough to warrant discontinuing therapy. Nasopharyngeal cultures were taken frequently and in the aureomycin-treated patients all were negative for *H. pertussis* after the third day of therapy. Among the twenty-two patients who did not receive aureomycin, there were twelve who had positive cultures on or after the seventh hospital day. There were no deaths in either group, and otitis media occurred in one patient who did not receive aureomycin. Weinstein[183] recently studied nineteen patients with whooping cough, thirteen of whom were under 10 months of age, and could not confirm the beneficial effects reported by Chang and associates and others.

In a small number of patients observed in our isolation ward, the effect of aureomycin may have been beneficial but was not sufficiently so to warrant its use routinely. The experimental results are in sharp contrast to equivocal clinical observations. Alexander and associates[76] reported aureomycin to be effective against *H. pertussis* in vitro, while Bradford and Day[72] demonstrated its effectiveness in experimental murine pertussis.

H. INFLUENZAE INFECTIONS

Meningitis due to *H. influenzae* is a very serious illness of infants and children. Inasmuch as aureomycin is effective in vitro and in mice experimentally infected,[46, 47, 76] it was tried in the treatment of meningitis in spite of the marked improvement in results over previous years with sulfadiazine, streptomycin, and specific antiserum. The small series of six patients reported by Chandler and Hodes[47] and the seven of Drake and co-workers[46] are sufficient to suggest favorable clinical response when aureomycin is used alone or in combination with sulfadiazine, but despite clinical improvement, one is impressed with the persistence of positive spinal fluid cultures—in some instances as long as five days after beginning therapy.

In our experience with ten patients, intravenous and/or oral aureomycin alone or in combination with sulfadiazine has not been as effective as a combination of streptomycin and sulfadiazine. With aureomycin, spinal

fluid cultures have remained positive for longer periods even though improvements in temperature, cerebrospinal fluid white count, and general condition have occurred. It would seem that aureomycin in this disease has a very definite bacteriostatic effect but only a slight bactericidal one. However, aureomycin may be valuable as an adjunct in the treatment of resistant or complicated *H. influenzae* meningitis. The first case in our series was one in which the meningitis was complicated by a subdural collection of fluid infected with *H. influenzae*. This cleared only when aureomycin was added to the therapy which had included streptomycin, sulfadiazine, and antiserum. Recently, the greater effectiveness of chloramphenicol in this disease has been suggested by Prather and Smith.[184]

In *H. influenzae* respiratory infections aureomycin has proved effective. In our hands a small number of cases of laryngotracheitis due to the microorganism probably has responded favorably to aureomycin in combination with sulfadiazine. However, in seriously ill children multiple agents have been used simultaneously. Braley and Sanders[185] treated eight patients with conjunctivitis due to *H. influenzae* and reported disappearance of the purulent discharge in all patients within twenty-four hours.

URINARY TRACT INFECTIONS

Aureomycin is of particular value in the treatment of genitourinary tract infections for the following reasons: (1) it is active against the most common infecting microorganisms, (2) development of drug resistance is infrequent, (3) toxicity is low, and (4) high urinary concentration can be achieved. Inasmuch as aureomycin is more effective in acid than alkaline media, it is advisable to keep the urine acid. The treatment of acute infections with aureomycin is highly satisfactory. In the management of chronic renal infections in children it is important to search for, and correct if feasible, anatomic defects. Urinary tract obstruction with stasis is the chief factor responsible for the chronicity of these infections. As is the case with other antibiotics the appearance in the urine of secondary invaders after eradication of the original microorganism still occurs. However this event appears to be less frequent following aureomycin. The two microorganisms most commonly encountered in long-standing cases, *Proteus vulgaris* and *Pseudomonas aeruginosa*, are resistant to aureomycin.

Most of the reports in the literature deal with adults who have had chronic urinary tract infections and failed to respond to one of the sulfonamides, penicillin, and streptomycin, either singly or in combination. Inasmuch as the same microorganisms are encountered in children, a similar therapeutic response is to be expected. Collins and Finland[186] reported on sixteen selected adult patients with severe, chronic urinary tract infections which had failed to respond to previous therapy. Fifteen had underlying defects of the urinary tract. During aureomycin therapy the urine cultures were sterile and the patients showed marked symptomatic relief. Shortly after discontinuing the drug, infection recurred in most instances. Others[11, 13, 27, 63, 187] have reported similar experiences in the treatment of chronic,

mixed, or intractable cases of urinary tract infections. Rutenburg and associates[9] treated eighty-nine patients having acute and chronic urinary tract infection with aureomycin and reported a satisfactory response in seventy-three patients. Clinical improvement was evident within forty-eight hours following initiation of therapy regardless of the sterility of the urine. Treatment was given for five or six days or longer if bacilluria persisted. Aureomycin was discontinued at the end of two weeks, and the case was considered a failure if the urine was not sterile at that time. The microorganisms which persisted in the urine usually were found to be resistant to aureomycin in vitro. Development of bacterial resistance occurred in two instances during therapy: a 43-fold increase with one strain of *Ps. aeruginosa* and a 4-fold increase with a strain of *E. coli*. In sixty-five patients the urine became sterile and remained so after the drug was stopped. In six patients recurrences responded to second courses of aureomycin. Of fourteen patients where only one microorganism was isolated from the urine and in which treatment failed, *Ps. aeruginosa* was the etiological agent in ten, *Pr. vulgaris* in two, *E. coli* in one, and *A. aerogenes* in one instance. Most of these strains when tested in vitro required more than 200 μg per milliliter for complete inhibition of growth.

SKIN DISEASES

The beneficial effects of oral aureomycin in the treatment of pustular lesions of the skin due to susceptible microorganisms is well known. It is of particular value in those lesions due to penicillin-resistant *Staph. aureus*.[24, 180] Although there are a few studies on the relative effectiveness of local versus systemic administration, one would suspect that local therapy has definite limitations.

The place of aureomycin in the treatment of venereal diseases will require a number of years for final assessment. At present, one can merely speculate as to whether it will augment or in certain instances replace penicillin in the treatment of congenital syphilis. Rodriquez and associates[29] studied the effects of aureomycin (70 Gm. in eleven days) in twenty-seven patients with syphilis, all having positive dark-field lesions. They observed the effect of aureomycin in eradicating the surface spirochetes from sixteen patients and found an average time of thirty-nine hours. This period of time appeared to be longer than that following therapy with trivalent arsenic compounds or aqueous penicillin. Secondary lesions involuted completely, and a satisfactory serologic reversal was noted. Healing of the late lesions of cutaneous syphilis with oral aureomycin has been noted in two patients,[80] and O'Leary[188] has reported encouraging results in neurosyphilis. Aureomycin has a definite place in the treatment of lymphogranuloma venereum and granuloma inguinale.[79, 87, 110, 111]

The oral administration of aureomycin in viral diseases which have skin manifestations has been partially explored. In this connection it may be of historical interest that lymphogranuloma venereum was the first virus disease of man treated successfully with aureomycin.[110] Finland and associates[104] treated twenty-four patients with herpes zoster. It was

observed that aureomycin halted the progress of this disease and brought about rapid healing of the lesions. The pain accompanying the acute lesions subsided after the first day of therapy and no new lesions appeared after this time. Postherpetic pain was not prevented in the patients in whom treatment was begun more than two weeks after the first appearance of the lesions. As stated in Finland's report,[104] the appearance of herpes zoster in a small number of patients while receiving this antibiotic[139] may result in a revision of opinion as to the specific value of aureomycin in this disease. A completely negative result with aureomycin in forty-one patients with varicella treated at the Willard Parker Hospital was reported by Mazursky and collaborators.[143] It is of interest that two patients developed epidemic parotitis despite the administration of aureomycin early in their incubation period. The drug has been reported to be useful in the treatment of ulcerative stomatitis[149] and Kaposi's varicelliform eruption[102, 189] although one patient treated at this hospital developed the eruption while on aureomycin and succumbed.[24] Eczema vaccinatum (one case) has responded well.[101] Plantar warts have been reported to respond favorably.[113, 114] Equivocal reports in diseases of unknown etiology can be found. Downing[190] states that pemphigus responds with indefinite success. There are two favorable case reports on the treatment of molluscum contagiosum[151, 191] although aureomycin therapy did not influence the course of the disease in one child treated in this hospital.[24]

BRUCELLOSIS

Although there still is controversy over the actual incidence of brucellosis in the younger age groups, the reported incidence is low; only 7 per cent of the cases reported in the United States Registration Area occurred in individuals less than 15 years of age.[192] Treatment has been very unsatisfactory until the recent advent of combined streptomycin and sulfadiazine therapy. It appears that this form of treatment usually is surpassed by aureomycin regardless of whether infection is due to *Br. suis*, *Br. abortus*, or *Br. melitensis*, although Green and Stein[214] reported three cases of *Br. suis* infection which responded poorly to aureomycin therapy. Relapses, although less frequent than with former modes of therapy, still occur. The first patient treated successfully with aureomycin was reported by Schoenbach and associates[38] who later added four additional patients.[193] A few of the many reports on the effectiveness of aureomycin are those of Woodward,[6] Spink and coworkers,[28] and Knight and collaborators.[194] Herrell and Barber[195] recommend the use of aureomycin combined with streptomycin or dihydrostreptomycin, based on evidence obtained by Heilman[196] who found this combination to be the most effective method of treating experimental brucella infections in mice. The majority of the reported cases are in adults and for this reason the case of Boyd and Prignano[197] is of particular interest. This patient, a 9-year-old girl residing in Connecticut, apparently contracted the infection while abroad. She was acutely ill for approximately six weeks before hospitalization and for

the first two weeks in the hospital, at which time the diagnosis was made by the isolation of *Br. abortus* from blood cultures and positive agglutination reactions in a 1:640 dilution. During the first five days of hospitalization she received penicillin and streptomycin without effect. When aureomycin (1.25 Gm. per day) was started on the fourteenth day she showed a marked improvement, all her symptoms disappearing within four days.

SALMONELLA INFECTIONS

Although the Salmonella are sensitive to aureomycin in vitro under certain experimental conditions, clinical response has been disappointing. In experimental *S. typhi* infections, Price and associates[17] found aureomycin to be only one-one hundredth as effective as streptomycin on a weight basis. When aureomycin was first employed in the treatment of typhoid fever, evaluation was difficult because the response was either slow or doubtful, with an occasional patient showing striking improvement.[39, 63] In some instances, there was rapid clearing of the bacteremia, and the stool cultures became negative; nevertheless, the patients remained acutely ill. As more patients were treated, it became clear that aureomycin exerts only a slight beneficial effect in some cases.[8, 13, 24, 118, 174] Similar experiences have been reported with other Salmonella infections. Chloramphenicol appears to be a more promising antibiotic in the treatment of Salmonella infections.[7, 8, 24, 118, 174]

SURGICAL INFECTIONS

Intra-abdominal infections usually are mixed infections with *E. coli* the predominant microorganism. The wide spectrum of activity, the availability of an intravenous and oral form, and mild side reactions make aureomycin a useful drug in the treatment of intra-abdominal infections. Unlike penicillin, aureomycin is active in the presence of pus and necrotic tissue.[9] The list of favorable reports on the use of aureomycin in patients with generalized peritonitis is large as are the total number of patients treated by different authors.[9, 14, 27 91, 198-200] Aureomycin has been successful in peritoneal infections in which other antibiotics failed.[9, 91, 198, 199] Yeager and associates[198] reported excellent results in sixteen patients with peritonitis. They suggested that aureomycin may have an advantage over penicillin or penicillin plus streptomycin in the treatment of peritonitis of postappendiceal origin. It should be remembered that the application of sound surgical principles, plus the use of fluids, electrolytes, plasma, transfusions, etc., is extremely important in treatment, and to overemphasize the antibiotic appears ill advised, particularly since penicillin and sulfadiazine have yielded spectacular results in the hands of some surgeons.[201] Although there is no agreement as to the most effective antibacterial agent in the treatment of acute peritonitis, most authors appear to favor aureomycin with or without the addition of penicillin. As judged by experimental studies of induced peritonitis in dogs, aureomycin is preferred to penicillin by Schweinburg and associates[202] although the survival rate in comparable experiments with these two antibiotics is about the same.

The preoperative administration of aureomycin in patients awaiting intestinal surgery is a useful procedure.[9, 52, 203] It also has proved useful in patients with biliary tract infections requiring surgical intervention. Varying degrees of success have been reported in the treatment of patients with ulcerative colitis. Rutenburg and collaborators[9] found aureomycin of no special value in the treatment of the acute exacerbations of ulcerative colitis unless peritonitis develops; in which case it seems to be of substantial benefit. More encouraging results were obtained by Strax and Wright[203] who reported a 50 per cent reduction in the number of bowel movements with the disappearance of gross blood from the stools in eleven of thirteen patients treated. In two children observed in this hospital, aureomycin did not significantly influence the course of the disease.

The usefulness of aureomycin extends to the treatment of a wide variety of surgical infections, many of which had failed to respond to other antibiotics. Aureomycin is not a substitute for surgical drainage of localized abscesses although its use often decreased the necessity for this procedure. Rutenburg and associates[9] present thirty-three patients with a wide variety of such infections including wound infections, osteomyelitis, cellulitis, acute parotitis, etc. In twenty-six patients the response was good, in five doubtful, and in two poor. Logan and collaborators[204] treated eighty-two patients with soft tissue infections with good results in all but one patient. Marked improvement in a few patients with lung abscesses also has been reported.[11, 179] In two patients with brain abscesses due to *Staph. aureus* and *E. coli*, Long and co-workers[14] reported satisfactory results. The use of aureomycin in skin infections has been mentioned in the section dealing with staphylococcal infections. A report on the favorable use of a 3 per cent aureomycin ointment in the treatment of fifty patients with a wide variety of pyodermic infections has been reported by Siegel and Schantz.[205]

ORAL INFECTIONS

The effectiveness of therapeutic trial in infections of the oral cavity is difficult to determine in view of the diverse mixed and frequently undifferentiated etiologies of such conditions. Greenblatt and associates[206] reported that fusospirochetosis (Vincent's infection in association with granuloma inguinale) responds more slowly to aureomycin than to penicillin therapy. Distelheim and Sulzberger[207] have reported a remarkable response in a case of chronic aphthous stomatitis. Herpes stomatitis has been reported to respond to aureomycin therapy[103] while stomatitis ulceromembranosa acuta has been reported as showing little or no response.[149] Jacobs and Jacobs[208] reported on the oral aureomycin therapy of twenty-five cases of oral infection, including such diagnoses as acute periostitis, subperiosteal abscess, gingivitis, mandibular osteomyelitis, etc. Although bacteriologic diagnosis was not made, these cases are of interest in view of the mixed etiology usually found in such cases. Surgical intervention was practiced when indicated. Four cases which responded to aureomycin had not responded to previous surgical

and penicillin therapy. In this entire series the results of aureomycin therapy were reported as excellent in sixteen, good in six, and fair in two cases.

RICKETTSIAL INFECTIONS

The reports from various countries on the aureomycin therapy of a number of rickettsioses have been uniformly favorable.[13, 27, 99, 100, 115-125, 212] The consensus of these reports is that aureomycin is superior to any of the older therapeutic agents, including para-aminobenzoic acid. Chloramphenicol also appears to be effective in rickettsial infections. Prognosis is improved even in the most severe cases if therapy is begun within a week of onset. Prolonged therapy often is advocated in order to prevent relapse which may occur when antibiotic therapy is discontinued early.

SUMMARY

This brief review of the pharmacology, antibiotic activity, bioassay, and clinical effectiveness of aureomycin is based on a number of the reports in an already voluminous literature on this antibiotic, together with some of the experiences of the staff of the Children's Medical Center. Emphasis naturally has been placed upon the use of aureomycin in the therapy of those infections encountered in childhood. The publications of the Lederle Laboratories[212] should be consulted for a comprehensive summary of the entire literature.

The majority of the reports in the literature are remarkably uniform as regards the range of clinical as well as experimental effectiveness of aureomycin. Its ready absorption from the gastrointestinal tract, freedom from serious toxic effects, and its unusual range of activity make aureomycin one of the most generally useful antibiotic available today.

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Psychologic Aspects of Pediatrics

SOME INTERVIEW TECHNIQUES IN CHILD PSYCHIATRY

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CONDUCTING a psychiatric interview, like taking a medical history and doing a physical examination, requires a thorough knowledge of the subject in hand. Nevertheless, the physician, without special training in psychiatry, can carry on a revealing interview if he is cognizant of certan facts and techniques and is willing to try to utilize them. Too often the pediatrician considers this aspect of his examination as too subjective and nonscientific and outside of his domain.

AIMS OF THE INTERVIEW

The purpose of the interview is to discover the nature of the child's problems and preoccupations, the sources of his worries and anxieties, and the manner in which he deals with them. The interview should provide information regarding two large areas of the child's personality: First is a study of the child's interpersonal relationships, his attitudes and feelings toward members of the society in which he lives. Second is a study of the child's fantasy and unconscious life. The child should be helped to give this information without creating undue anxiety, pain, or fear.

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The attitude of the physician during the interview is important. He must show a genuine interest in the patient. Every effort should be made through facial expression, tone of voice, and physical contact to establish a friendly and secure relationship with the child.

An interview is therapeutic as well as diagnostic and can do harm as well as good. If improperly conducted, it may provide some diagnostic material but it may harm or prolong future therapeutic efforts. After the information has been obtained, the findings must be interpreted so that they can be fitted into a diagnostic and therapeutic scheme.

The interview may be regarded as a test situation to which the patient is expected to respond or react. This is the basic principle of all psychologic testing. Thus the interview may be formal and systematic with specific questions being asked. The replies may be compared with norms arrived at statistically and evaluated accordingly. Or, the interview may be flexible, the patient talking about anything at will without the physician attempting to channel ideas, concepts, or thoughts. This is the so-called "free-association" technique. In dealing with children at the first interview, it is usually advisable to steer between the above extremes. Each

child must be considered individually. If the child in answer to a question spontaneously goes ahead with a flood of ideas and associations, it is wise to listen and pick out the significant findings; to let the flood drain itself, and not to interrupt him. On the other hand, where the child's verbal spontaneity is less active, it is advisable to encourage and stimulate him, to tap the different areas of his personality by further questions.

A number of aids are available to help the child tell us what he wants to. Lately, there has been a growing distrust in psychiatry of purely verbal methods. New approaches, such as projective techniques, supplement but cannot replace the interview. This is particularly true in children. It should be emphasized that every child who can handle language (i.e., aged 3 years and upward) can express his inner, hidden mental processes as well as his conscious strivings and desires at a verbal level, without necessarily resorting to highly specialized techniques of play therapy, puppetry, projective testing, etc.

BEGINNING THE INTERVIEW

To begin with, we should introduce ourselves to the child and tell him our purpose. A good way to start is to ask him why he thinks he has come, or why he thinks he was brought by his mother or guardian? Usually, he can be started by asking for only one possible reason. In some cases it is necessary to be indirect to the extent of postulating why another totally unrelated child might be brought. Some children are quite ready to talk about their problems providing it seems that someone else is being discussed. The important thing is to try to get the child to talk. Every time the child says something, it may indicate a possible difficulty and it should lead to another appropriate question. Very often mere repetition of the child's last reply may foster further comments by him.

INQUIRY INTO INTERPERSONAL RELATIONSHIPS

It is usually advisable, in the early part of the interview, to ask specific questions regarding the child's interpersonal relationship. We should ask about his home. Where is it? Who lives there? Then we can ask him to tell us a little about the members of his family—his attitudes and feelings toward them. A question such as "Tell me something about your father?" or "What is a mother good for?" may be extremely productive. If a child considers that his mother is punitive, hostile, or nervous, this has great significance even though his estimate may be erroneous. This is so because the child's feelings and his reactions to them are what usually create his problems. Questions should be directed at attitudes toward siblings, parental preferences, and relationships to contemporaries. The latter include friendships in the neighborhood as well as classmates. The child's adjustment in school is important. Often he will readily express his pet interests and hobbies, his future ambitions, and his attitudes toward his teachers. In studying these interpersonal relationships it is important to find out what the child thinks about himself—does he have inferiority feelings? Does he recognize his abilities? What does he think he'll grow up to

be? The child's attitude to the examiner should also be noted. Is he shy, meek, and introverted? Does he cry and shun the examiner or is his attitude aggressive or hostile?

INQUIRY INTO UNCONSCIOUS AND FANTASY LIFE

The next area for investigation is the child's unconscious and fantasy life. Here we often make use of some special techniques. Essentially each strives to tell us what the child is thinking about. The child remains unaware that he is imparting to us highly relevant, emotional material. Whereas the child's verbalizations regarding his interpersonal relationships can be readily interpreted, this intrapersonal or unconscious material is more difficult to evaluate, and requires clinical experience and some knowledge of psychopathology.

A study of any phobias or fears is important. Often these may be indicated by asking the child to describe the worst thing that could possibly happen to him. This may be so frightening that he may be unwilling to talk about it, yet he may suggest drawing it and of course this should be permitted.

In the three wishes we say to the child, "Suppose you had three magic wishes and could wish for anything at all that you want, what would you wish for?" This may give an idea of secret desires, suppressed wishes and cravings and may even indicate basic dynamics as is shown in one of the cases cited below. Dreams provide an important source of information. The child should be encouraged by remarks such as "surely you can tell me only one dream." If he offers a "bad, scary" dream, a "good, happy" dream should be asked for. If he repeatedly denies dreams, one can ask him to make it up out of his head. Despert[1] has recently indicated that these invented dreams are as valid as real ones especially in children of preschool age. Children having nightmares or night terrors are only too happy to share them.

Another device is to postulate a deserted island upon which the child in a magical way is stranded and then to proceed to find out whom in order of preference he would like to take along with him and whom he would prefer to exclude if he had his own way completely.

Still another, is to have the child make up a story, good or bad, or have him complete a story you have started. In this story, the information already obtained can be used to procure more.

The routine psychiatric interview in an adult includes the investigation of delusions and hallucinations. Children rarely object to being asked if they ever hear noises or voices in their heads or elsewhere. The more direct and straightforward the question, the more clear-cut the answer. Children who are asked about their "imaginations" are glad to talk about them. They will eagerly discuss imaginary companions and playmates, etc. This is a normal developmental phase and is most frequently found about age 3 or 4 years. It has pathologic significance only if it persists (fixation) or is reverted to at an older age level (regression). Even at the 3-year-old level, the child shows in many ways that he distinguishes between his real world and his imaginary one. In abnormal cases, this distinction between

reality and unreality is not as clear. Delusions in children under 10 years of age usually take the form of introjected bodies. These may include good and bad devils in their heads or stomachs, etc. Pointing to the appropriate anatomic area and asking "what's in there" may bring answers ranging from "food and brains" to "God, superman, devils and fire engines, etc."

Delusions in children above the age of 10 years usually take the form of projective phenomena and are often paranoid in nature. They are harder to elicit because the child is more suspicious and more guarded. This change from introjective to projective phenomena is thought to be maturational. Both may exist simultaneously. As the child who is mentally ill gets older, the devil in his stomach or in his head who is telling him to do bad things is externalized and an outside voice or other person replaces it. This external force tells him what to do, or controls his mind, or says bad things about him.

Questions may be directed at the child's orientation with regard to space, time, and his physical surroundings. Does he feel that he is changing in size? Does he have abnormal bodily sensations? Do the walls seem to change and to close in on him? Does he have bizarre concepts of time and what are they?

Another area to investigate is the child's conscience (superego structure). Does he know right from wrong? Does he have guilt feelings? Why is it bad to do things his mother has complained of as being bad? Does he manifest anxiety about doing bad things?

EVALUATION OF INTELLIGENCE

Still another aspect to be covered in the interview is an evaluation of the child's intelligence. Often the reaction to the questions, the logic of the answers, the vocabulary used, and the methods for self-expression are revealing. In addition, the pencil and paper tests referred to below should be of value.

PENCIL AND PAPER TESTS

While the verbal interview is going on, other techniques especially the pencil and paper tests can be used.[2] Bender-Gestalt cards[3] may be presented, draw-a-man,[4, 5] draw a house, person or tree,[6] spontaneous drawings, all may offer special material of value. Preoccupation with these activities may make the child more relaxed and thereby facilitate his spontaneous verbalizations. The child may be, so to speak, caught off his guard.

MOTOR PLAY AND MOTILITY PATTERNS

Whereas the pencil and paper work may be more helpful in the older child, physical contact is very important, especially in the preschool child. At this age level, it is really inseparable from the verbal interview. One facilitates and is intimately linked up with the other. Thus the child can be questioned while sitting on the physician's lap or resting in his arms. Also, questions can be periodically interspersed with efforts at engaging the child in some type of motor play. Often, the closer the physical contact, and the greater the amount of motor play, the more successful will be the verbal interview. In some young children, no verbal contact can be effected at all until a physical relationship has been

established. Whereas young children normally and older children with schizophrenia enjoy whirling, rotary, motor play and derive extreme pleasure from it, children with organic brain disease resist being tossed about manifesting extreme anxiety.[7, 8] In this way, a considerable amount of the child's neurologic status can be assessed. Plasticity, cohesiveness, impulsivity, hyperkinesis, motor tone, muscular power and development, twitchings of muscle groups, and reaction to gravitational changes can all be evaluated. Above all, most of this information can be obtained in the space of about one-half hour, easily within the limits of the pediatric consultation.

The interviews which follow are presented to illustrate some of the principles previously discussed. It must be pointed out that interviews with the parents are usually necessary, as well, to give the physician a more complete picture of what is going on. Both children discussed below were interviewed privately, the parent having been sent out of the office after the initial complaints and history of the present illness were taken. Although many feel that all interviews with children of any age should be private, I feel that this has to be individually evaluated. At times, with very young children, it may be beneficial to have the mother present as a source of comfort and security to the child. At other times, with older children, this technique may be used for part of the interview to see what reactions it may provoke in both the mother and child. The following interviews were recorded in shorthand on initial contact with the child. The first case interview has been chosen to illustrate pathology largely in the sphere of interpersonal relationships, the second to indicate pathology in the unconscious and fantasy life of the child.

CASE PRESENTATIONS

CASE 1.—A. D., a 10-year-old white boy, was brought by his mother because he was adjusting badly in school for the past year. He was having frequent nightmares, spending much of his time daydreaming, and fighting and arguing frequently with his sisters.

(My name is Dr. Caplan and we are going to try to talk about some of your troubles.) Yes.

(How old are you?) 10—in March.

(You just had a birthday a little while ago?) Yes.

(Get any good birthday presents?) I got money. I put it in the bank. I have to save it for birthdays for my mother and grandparents also.

(Can you buy anything for yourself with the money?) I bought a game.

(Who stops you from buying things for yourself?) Nobody.

(Tell me—how did you happen to come to the clinic?) My mother brought me two weeks ago.

(What were the reasons for it?) I don't know.

(Can you tell me one thing that could be the possible reason?) She told me something about daydreams. I have nightmares.

(Can you think of any other reasons?) School.

(What about school?) I daydream in school.

(Do you like school?) I used to love it in the first four grades. I got a medal for good conduct. I am in

the fifth grade now. The teacher is too strict.

(Your teacher is too strict?) What? Yes. You know if you fall asleep she picks up your head and hits you. Nobody was ever hit in the lower grades; but in this grade, if you fall on the floor, you get hit.

(Is this trouble only with you?) The best ones get it too if they don't know their lessons.

(Do you think your teacher is the reason you are not so good in school?) No. I daydream.

(Did you used to daydream before?) No. I just close my eyes. At night I never sleep. I cannot sleep at night. I go to bed late and get up early. I fall asleep about 10 or 11 o'clock.

(How early do you get up?) About 6 o'clock.

(Do you feel that you have to daydream?) I don't have to.

(Do you daydream?) Yes. I just go to sleep.

(That's not daydreaming.) I don't know.

(What other troubles do you have?) My mother is always mad.

(What makes her mad?) My father. My father calls up and my mother starts yelling. They have a legal separation.

(How long have they been separated?) From January.

(What does it mean "separation"?) They cannot see each other. They could see each other but they cannot sleep together. I don't know what it is. They don't have to sleep together. It is just like—They don't have to. I don't mind my mother's business.

(How does this problem worry you?) She says to the children after she is on the phone, "He is always calling up and bothering me."

(You mean your mother gets cranky?) Yes.

(She seems a little more mad?) When she sees my father go out with another girl, she is happy. She is glad she saw it.

(You mean otherwise she doesn't know where he is all the time?) Yes.

(You have no other troubles beside the ones you mention?) Not that I can remember.

(How do you get along with your sisters and brothers?) I don't have brothers, just two sisters.

(How old?) One is 12 in the seventh grade and one is 6 in the first grade.

(How do you get along with them?) I get along. I argue with them but we don't really fight. I am spiteful.

(How are you spiteful?) I get mad. I send away for things on the radio and television. I hardly ever get them. I get mad.

(What does spiteful mean?) Being mean. When my sister gets things that I don't, she never shows me.

(How much do you play with other children in the street?) I don't go in the street. I go in the park.

(What games do you play?) Baseball, football, and swimming.

(You were telling me about nightmares.) The worse one was in October, two or three years ago.

(You still remember it?) Yes. I was asleep—dreaming of something—I don't know what about. Then I heard a noise and I woke up right away and I looked at the closet and I saw a door opening and a man hits me over the head. Later I asked for my bed to be moved and changed after

that. My big sister got the same dream when she slept in the same place. She heard me talking about it so she dreamed about it.

(What did this man look like?) A rough man. With a big nose.

(Can you tell me another dream?) About my small sister. These are the ones I am having now. I am always telling her not to go places and she gets in trouble. She goes in the yard and I hear her yelling and then I wake up. I never complete any of my dreams.

(Do you wake up frightened?) Yes.

(Do you ever cry?) Yes.

(Who comes to you?) I run to my mother.

(Do you sleep with her?) No. My small sister is there. I make sure my sister is in my mother's room, when I go there.

(Do you have any happy dreams?) Sometimes.

(What would be a happy, pleasant dream to have?) I don't know.

(Make it up.) That I am a movie star. I would like to be a psychiatrist or a policeman.

(Is that your ambition?) Yes.

(What do you think a psychiatrist does?) He tests your blood. He asks questions like you are doing.

(Why does he ask questions?) To make you happy. I get a lot of things off my chest. I feel better.

(Can you remember all the things you got off your chest today?) Yes. Dreams, about my father, in school. My troubles.

(Do you ever tell anyone else about these things?) No.

(What sort of things don't you tell your mother?) My dreams.

(You don't feel free to tell her?) No.

(Suppose that you had three magic wishes and you could have anything you want?) One, I would like to have my mother happy, two, a house for my dog, and my third one is about sports—to be strong. I am not strong in baseball—the most I can do is pitch. I get tired.

(Have you got a dog?) A fox terrier.

(Have you always had a dog?) Not always. I had one four months ago. I had two dogs.

(What happened to the dog?) He was poisoned. Someone in my building. They didn't like his barking. He was out in the yard. I cried to myself.

(How often do you cry to yourself?) About once a month.

(Do you feel better after?) I feel the same. Not worse.

(Did you try to get even with the man for poisoning your dog?) I imagined I was a secret investigator.

(What sort of imaginary games do you play?) My friend plays the games. We play pirates. For pirates we hide several things.

(Suppose you were marooned on a deserted island. Whom do you wish you could take along with you?) My dog.

(Anybody else?) No.

(Suppose you had to get somebody else?) My mother.

(Somebody else still?) My smaller sister. My smaller sister could come through things easier. She is very good at digging. She showed me how to swim. She is always teaching me. Next my big sister.

(How about your father?) I would take him.

(Would you be very anxious to take him?) No.

(I take it that you don't like your father as much as the others?) No. It's not true.

(Maybe you are worried how your mother would feel about it?) No.

(What sort of man is your father?) He works as an electrician.

(Is he good?) Yes. I used to help him work sometimes.

(Did you enjoy working for him?) Yes. I got $21.

(How often do you see him?) I see him once in a while. Three times a week. He meets me outside of school. I don't go any place with him.

(Did you ever visit his girl friend?) I saw her once.

(Did you like her?) No. She liked me. Her husband ran away.

(Why didn't you like her?) I would like my family to be together.

(Who is the troublemaker?) The woman.

(How can she make trouble?) She always wants to see my father. She makes my mother mad. There are so many things about her. She is Spanish. My mother hates the Spanish language even.

(What do you think makes a father go away?) I think it is the woman. That is why I don't want to get married, because if you marry one girl you always want another. You always get tired of one. If you see a pretty girl then you see a prettier one.

(What does prettiness have to do with it?) I don't know.

(So you plan never to get married?) No.

(What will you do when you grow up? How can you have a family?) I won't, I don't care at all.

(How do people get children?) From the stomach. Like my mother. I don't know, my mother just told me from the stomach.

(How do dogs get puppies?) Same as human beings only they don't have to take long. I go to sleep one night. The next day you look, you see puppies—that is what happened to my uncle's dog.

(Do you think you are nervous?) Yes I think so.

(How do you feel?) My mother wrote you a note about it.

(Do you want me to read it to you?) I don't care.

(I see you bite your nails?) Yes.

(Does it make you feel better?) No. I feel worse when I bite them too far down. I bit it too far down and it hurts, whenever I press my finger.

(What do you think is inside your head?) Brains.

(Anything else?) No.

(Did you ever think there were noises inside there? Do you imagine things?) No. I imagine things—my dog Skipper—whenever I look at him I think of Blackie.

(Do you know it is not Blackie?) I know. But I like to imagine it.

(What other things do you imagine? Do you ever imagine your father is back home with you?) No.

(What do you think is inside your stomach?) Food. Also I am fat there.

(Do you think you have too much fat?) Yes. I look on the scales. If you are 5 feet 2 inches, you are supposed to weigh so much. I weigh so much. I weigh 118. Its about right but I look like I am overweight.

(Do you think your mother is a nervous woman?) No.

(Would you like to come back and see me again?) Yes.

(Our time is nearly up. Any questions you would like to ask?) No.

Discussion.—This case illustrates pathology in the field of interpersonal relations in a 10-year-old boy. Thus we see difficulties in his relationship to his siblings, in making friends, and in getting along with them both at home and in school. In addition, he has difficulty in his relationships to himself. This is indicated in his marked inferiority feelings about his ability in sports and about his obesity. He tells us in one of his three wishes that he wants to be strong and good in baseball. Further we see the difficulties created by the broken home and the various ambivalent and conflicting drives with which he is faced in regard to his mother and father.

It must be emphasized again that this boy, although under great tension at the time of the interview (his father had threatened to take him away from his mother that very day), was able to talk about extremely troubling personal problems to a stranger with relative ease and openness.

The verbal content of the interview and the way in which the boy related and controlled himself revealed that the problem is a neurotic behavior disorder. This is usually the case where the pathologic findings are in the field of interpersonal relationships. Furthermore, on the surface of things it appears that the problems have been created both at home and in school by environmental factors. Faced with a split between his mother and father and with nobody near him to whom he can turn for help, he has taken to daydreaming as a means of escape. Thus the daydreaming is a defense mechanism for him which he uses to help cope with his problems. The physician in his therapy of the case can fill this need of someone to turn to for help. Also the daydreaming has obviously aggravated his maladjustment in school.

In the interview he tells us clearly what his attitudes are to his mother, sister, father, and the mistress. His dreams are also revealing of his basic problems. They are anxious and frightening. In the dream where he is worried about his sister getting into difficulties, and where he tells her not to go to certain places but she persists and finds trouble, we see his preoccupation over his sister's welfare. An understanding of dreams and their meanings and of the workings of the unconscious reveals to us the possibility of feelings of hostility and guilt toward her. We have already seen from the mother's original complaints that there was an exaggeration of the normal problems of sibling rivalry with regard to his sister. However, the finding of this problem in a dream is more important than the mother's statements. How deep this problem is and how important it is to the child can be discovered only in further interviews.

From the material provided it also seems that the boy shows some blocking on sexual matters. This may, however, be because of lack of sufficient rapport with the examiner, or it may reveal problems pertaining to preadolescence.

It can be seen that some of the questions are quite straightforward and pointed, e.g., "I take it, you don't like your father as much as the others?" Such a question is not necessarily traumatic. It depends on

how it is put. Sometimes such a stress situation may help evaluate the child and his reactions. His answer to the question is probably truthful. He does like his father. This is the crux of his difficulties. He likes both his father and mother and they are split up. The interview shows how greatly the boy has identified with his father. He absolves him from blame saying it is all the fault of the woman. He even says that when he grows up he too will follow in his father's footsteps, for if he would marry, a prettier girl would come along and he too would have to leave his wife.

It is well known from clinical work with children that animals in the child's language and thought often represent some member of the family circle. The same animal may represent to the child a sibling, or a mother, or a father at varying times. Probably the reason that most children take so readily and easily to animal pets as close companions stems from this need of the child to be close to a parent substitute that he can control and direct at will. This fits in intimately with his basic needs and drives. Thus in wishing to have a house for his dog the psychiatric interpretation is that the child wants a home for his father. Incidentally, the three wishes in this case are revealing. In essence, they sum up his basic problems; his worry about his mother's unhappiness, his desire to have his father back in the home with him, and his inferiority feelings about his mild obesity.

CASE 2.—J. H. is a 6-year-old Negro girl. She was brought by her mother because she could not get along in school; she continually fought with the other children and felt that they were always attacking her. She went excessively to the bathroom, would not obey, had frequent nightmares, and talked to imaginary friends.

(Hello there, my name is Dr. Caplan.) You know what happened last night?

(What?) I saw a jungle picture on the television. People were sailing in a boat and they had a shipwreck and everyone had to sleep in the jungle and when they woke up there was a skeleton and I said "mother turn it off" and I was so excited and hollered in the night with my mother.

(Was that a dream?) It wasn't a dream. I saw it on the television and then dreamed about it. I don't know. (Then pointing to a shelf on the wall of the office) What's that little thing up there for? Is it for people to talk through like a window?

(Do you ever imagine things?) Yes. Sometimes I imagine I'm in the jungle. My mother saw another skeleton there, that was before the natives came along.

(What is a skeleton?) The skeleton. It is some old dead bones that when people go and they're dead for a long time they have a skeleton. The natives just leave those old things around and those old heads are hard.

(How do people die?) Because the natives kill them or something. Sometimes they die for no reason.

(Are you afraid of dying?) I hope I don't. I hope I don't. No. No.

(Have you any friends?) Miss Liberty. She is a statue. I'm not afraid of her. No she can't talk because she is just a statue but I can tell when she is around.

(Who is Alexander?) Did my mother tell you? The one is in my funny paper. The one who is my boy.

(Do you talk to him?) Yes. He throws things on the floor and bang slam. When he chases me upstairs I hear blappity, rappity, and rumble bumble.

(What's in here?—pointing to her belly) Some bones, blood, and juices. Its the place where my food goes. I imagine that I have two bones and a little and some blood and juices and little things hanging on to me and little fat meats inside and flesh under the skin.

(Anybody ever talk in there?) Except when I was talking to myself, I can feel myself talking back.

(What does it say?) It just says what a happy world and I think about my sweet land of Miss Liberty.

(What's in there?—pointing to head) My mother said there was a dragon or something in my head, that makes me think. When I am talking to myself I just feel my stomach talking back.

(What does it feel like?) It is like sometimes when I go to sleep I wake up early in the morning and I feel so hungry. All's I feel is just a little thing right there. It's a big hard bone. It feels just like a heavy juicy white bone.

(Ever dream?) Not much. All's I dream about is roses and stuff. My mother ran out and said she is having a nightmare to daddy. I ran out and cried. It was the part about the skeleton.

(What else scares you?) Skeletons and dark places.

(Ever have a happy dream?) A good dream is where everything comes out good, like the story in Cinderella, like a nice lovely place, like going to the country.

(Suppose you had three magic wishes?) I'd wish I had some little baby ducklings and a kitty cat and a doggie. I would play with them and let the little black kitten kiss them and play together. I would let him scare the cat and eat the rat. I wish I had some doggies, mules, and all.

(Who talks to you outside?) Nobody, I just think something's talking to me. I don't know how it comes into me. I guess it's just myself. I look all around and I could never find out. I just go to mother and just tell her. I tell her I hear something inside of me.

(What's the matter?) (Rubbing her nose) I feel like I sneeze. When I start to talk real fast I feel that little thing in my nose. (Again she points to the shelf on the wall.) I want to find out if that's a little thing that opens up and somebody talks to you. Will you go over and see if there is a room next door. I want to see if there is a hole in the wall.

(Does anything ever seem different to you?) Yes I go to people's houses sometimes and they seem to change. The look on their face is different. Sometimes we have so many people at home, visitors, I don't know who is who. I get all mixed up. (As she was leaving the office she said) I notice that I like the echo that comes from this building. It feels so good.

Discussion.—This case illustrates pathology in the field of the unconscious and fantasy life of a 6-year-old girl. The interview is more flexible and less rigid. This girl's amazing fantasies which she verbalizes extremely well are allowed to pour out. In fact, efforts to stem this productivity will fail because the child's

anxiety is such that she must persevere in this push of ideation, speech, and motor activity. The material produced shows marked precocity of a pathologic type. The picture is that of childhood schizophrenia and this is always a possibility when the pathology is in the field of abnormal fantasy and unconscious material.

The case shows the phenomena of introjected bodies, voices which talk to her in her belly, and abnormal sensations and feelings in various parts of her body. Thus she says that when she talks real fast she feels a little thing in her nose as if she were going to sneeze. Not only do things change within her body, but she also describes the feeling of things changing outside her body. People's houses seem to change, the look on their face is different. There are marked feelings of unreality and an inability to identify with other people. Because of this she feels that the children attack her and she cannot play or adjust to them in school. She also shows projective delusional and hallucinatory phenomena. Her imaginary friends and playmates talk to her. She can hear "Alexander" making noises as he runs up and down the stairs. Reality and unreality flow into each other without clear-cut distinction. This was seen in her discussion of the scenes on television and how she confused them with her dream life and vice versa. It is also seen in her relationships to her imaginary playmates. These are not always pathologic at this age. They gratify the need to identify with others and the need for constant satisfying relationships, but here the relationship is definitely abnormal and the distortion of reality is highly significant.

Another feature gathered from the interview and typical of childhood schizophrenia is the pathologic concept of her body image. Her belly consists of "blood, bones, and juices and things hanging on to her." She was extremely plastic and clung to me continually as she sat on my lap, her body practically melting and fusing with mine.

Also to be noted is the marked anxiety which the child manifests in her frightening fantasies, her nightmares, her free flow of speech and ideation, and the need to get security of some kind from a close bodily contact with others.

This interview has been used to illustrate how readily most bizarre phenomena can be elicited even in the very young age group.

SUMMARY

The technique of conducting a psychiatric interview with a child is discussed. The interview is treated from two main points of view.

1. *Investigation of interpersonal relationships.* This includes:

(a) Attitudes toward various members of the family, e.g., parents siblings.

(b) Attitudes toward contemporaries, at school and in the neighborhood.

(c) Attitudes toward teachers and other figures of authority; adjustment at school, and at other group activities.

(d) Attitudes toward the self, e.g., problems of inferiority, superiority, feelings of rejection, and so on.

(e) Attitudes toward the examining physician.

2. *Investigation of unconscious and fantasy life.* These include:

(a) A study of the dream life.

(b) A study of fears and phobias.

(c) A study of introjective phenomena.

(d) A study of projective phenomena.

(e) A study of the child's fantasy and inner dynamics through such methods as: the three wishes, imaginary figures, the deserted island, made-up stories, and other verbal projective techniques.

A description is given of supplementary pencil and paper tests and methods of physically contacting and examining the child carried out concurrently with the psychiatric interview.

Two illustrative cases with discussion are appended to illustrate pathology in the realm of (1) interpersonal relationships and (2) unconscious and fantasy life.

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Comments on Current Literature

VESICULAR STOMATITIS VIRUS OF CATTLE PRODUCING HUMAN DISEASE

THE importance of animal reservoirs of disease in human infection has been emphasized by numerous investigators, notably Karl Meyer[1] whose recent reviews have comprised excellent discussions of the entire subject. Dr. Meyer calls attention to many instances which stress the significant relationship between the findings of veterinary science and human disease, and has discussed the actual and potential dangers of "break-through" of such infectious agents from lower animals to the human population.

In the November (1950) issue of the *Journal of Laboratory and Clinical Medicine*,[2] Hanson, Rasmussen, Brandly, and Brown report the occurrence in three human subjects of infection with the virus of vesicular stomatitis. These infections occurred in the course of animal experimentation in which a strain of virus was used which had been isolated from a cow in October, 1949.

Vesicular stomatitis has been recognized as a disease of horses and cattle since 1915, and has been reported to affect swine also. While clinical observations have suggested for some time that the disease is transmissable to man through contact with animals, confirming laboratory studies were lacking, and definite etiology was not established. The present report by Hanson and his associates concerns studies carried out on three staff members who were exposed to the laboratory strain of virus, and whose illness was similar to that previously described, being characterized by sudden onset, myalgia, and fever.

The strain of virus being investigated in the laboratory had been maintained by routine serial passage in embryonated eggs or by intracerebral inoculation of mice in which death follows inoculation within forty-eight hours. Intradermal inoculation of footpads in guinea pigs induces swelling and redness. The characteristic disease in cattle, "vesiculation, maceration and sloughing of the mucosa" accompanied by "fever of 105° F. to 106° F., inappetance, and rapid loss of weight," can be produced experimentally by inoculation of virus suspensions from egg passage into the oral mucosa.

Of the three human cases reported by these authors, the third case presented all the salient features of the disease as it occurs in man, and is well documented from a laboratory point of view. All three patients had been working with the virus of vesicular stomatitis and all presented a similar clinical picture, manifestation of illness occurring thirty to forty-eight hours after exposure to the virus. The third case was of particular interest in that the time of known exposure was definite since this worker had been spattered with virus-containing material while harvesting allantoic fluid from experimentally infected eggs. Onset of illness was rapid with nausea and anorexia, myalgia, headache, chills, and high fever. Within twenty-four hours, two of the patients showed marked clinical improvement, although weakness continued to be a prominent feature.

However, a secondary rise in temperature occurred with recurrence of symptoms—malaise, myalgia, headache, anorexia, and chills—which continued for about two days. With the exception of persistent weakness lasting for a period of eight to ten days, recovery was prompt and complete. Except for the presence of stomatitis

which was described in two of the three patients, the physical findings were those associated with an ordinary upper respiratory infection. In the third case, the findings are of particular interest, since the authors give a rather complete description of the development of the buccal lesion. At the time of the initial rise in temperature a small red papule was noted on the buccal surface of the lower lip. By the time of the secondary temperature rise two days later, the papule had developed into a small herpetiform ulcer about 2 mm. in diameter, characterized by punched-out edges and a clean grayish floor, and surrounded by an area of intense erythema. The anterior cervical and submental lymph nodes were swollen and tender. With clinical recovery of the patient the oral lesions healed promptly without scarring.

In the first case, serum from a blood sample obtained several weeks before the illness was shown to be free of neutralizing antibody to the vesicular stomatitis virus. Serum obtained on the seventeenth and twenty-fifth days after the onset of the illness showed the presence of a high titer of specific humoral antibody to the virus. In the second case, a serum sample taken seventeen days following the onset of the infection was shown to contain specific neutralizing antibody, but no other serum samples were tested. In the third case, whose known exposure was definite, complete studies were carried out. Serum samples obtained seven days before onset and two days following onset of clinical manifestations showed no antibody to the virus of vesicular stomatitis, whereas a serum sample obtained ten days after onset showed significant titer of antibody, and one eighteen days after onset an even higher level of neutralizing antibody. These laboratory studies, particularly those carried out on the third case, present fairly conclusive evidence that during clinical recovery there was increasing titer of antibody to a known strain of vesicular stomatitis virus. Unfortunately, no virus was isolated from any of the patients observed.

The possible role of strains of virus as the etiological agent in ulcerative stomatitis in human subjects has prompted considerable clinical and laboratory investigation. The virus of herpes simplex has been implicated in a number of instances in which a strain of virus was isolated from affected individuals and in which laboratory studies demonstrated the presence of specific humoral antibody following recovery. Recently, however, Dodd and Ruchman[3] have described recurrent stomatitis in which apparently the etiological agent is not a strain of herpes simplex virus. The clinical entity of rhythmic neutropenia with recurrent ulceration of the buccal mucosa which recently has been brought to attention again[4] may prove to be of viral etiology.

Ulcerative stomatitis is a condition which lends itself well to objective clinical observation and to laboratory investigation. With more adequate laboratory facilities available, well-planned, carefully controlled studies will clarify eventually the etiological status of this confusing group of diseases.

RUSSELL J. BLATTNER

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News and Notes

The Pediatric Cardiology Department of the Children's Division of the Cook County Hospital of Chicago has fellowships available for immediate appointment During the past three years, over 500 cases of congenital malformations of the heart were studied. Salary commensurates with experience. Application and further information may be obtained from Dr. Rowine H. Brown, Children's Division of the Cook County Hospital, 700 South Wood St., Chicago 12, Ill.

The Boston Floating Hospital, the Pediatric Teaching Unit of the New England Medical Center, announces the appointment of Dr. Orvar Swenson as Surgeon in Chief. Dr. Swenson has also been appointed Associate Professor of Surgery in the Tufts College Medical School.

A virus research laboratory which will concentrate upon childhood infections has been established at the University of Louisville School of Medicine. Its completion was effected by a grant from the recently organized Kentucky Child Health Foundation. The investigations will be supervised by Drs. Alex J. Steigman and James G. Shaffer of the school's Child Health and Bacteriology Departments.

The Orthopaedic Hospital, Los Angeles, announces three short courses in polio for physicians during 1951, aided by a grant from the National Foundation for Infantile Paralysis. The courses will cover all phases of patient care with emphasis on teamwork among professional services. Demonstration of new apparatus and methods for acute polio will be presented through cooperation of the Los Angeles General Hospital. Classes are scheduled for: Feb. 12-15, May 21-24, and Oct. 22-25, 1951 (inclusive). For further information write C. L. Lowman, M.D., 2400 S. Flower St., Los Angeles 7.

Communication of the General Secretary, International Paediatric Association:

The third pamphlet of the Sixth International Congress of Paediatrics, with the missing abstracts of lectures, and all the communications and discussions, is finished. This volume will be sent to the different national paediatric associations for distribution free of charge among the conference members with cards series A and C who are requested to apply to their paediatric association in this matter.

All those interested in this literature, such as physicians, libraries, clinics, etc., may obtain either the 3 single volumes for Swiss francs 25.- or the 3 volumes bound together for Swiss francs 27.-. The congress transactions will be edited by the General Secretary's office, International Paediatric Association, and sent to the applicants after payment has been received. If more than 10 copies of the whole transactions are ordered, a reduction of 20 per cent, and if more than 20 copies are ordered, a reduction of 30 per cent will be granted. Orders may be forwarded to the General Secretary's Office, Kinderspital, Zürich 32. Payments should be made to the account of the association with the "Zürcher Kantonalbank," Zürich.

A certain number of the transactions of the Fifth International Congress of Paediatrics, New York, 1947, may still be obtained from Messrs. Almquist & Wiksell, Editors, Upsala, Sweden, for the reduced price of Swedish crowns 10.-.

Book Reviews

Speech Problems of Children. A Guide to Care and Correction. Prepared for the National Society for Crippled Children and Adults by the American Speech and Hearing Association. Wendell Johnson, Ph.D., editor, New York, 1950, Grune and Stratton, 265 pages. Price $3.75.

Leading speech correctionists and speech pathologists have collaborated in writing this book which should be very helpful to parents, teachers, nurses, and physicians interested in speech problems of children.

The introduction states that from 15 to 20 per cent of school children have speech problems and 5 per cent are in urgent need of speech correction. The opening chapters survey types of speech defects and the resulting effect on personality, trace the normal development of speech, and give advice on how parents, teachers, and the community can help the child who deviates from the normal speech pattern.

Chapters 4 to 11, inclusive, discuss in detail the types of defects, attitudes of parents and teachers, prognosis, and therapy. Children who "don't talk plain" (functional disorders of articulation) and children who are slow in learning speech are discussed first. The chapter on cleft palate and cleft lip deserves special mention as it offers such excellent advice to parents in accepting the handicap. The chapter on children with cerebral palsy gives special emphasis to techniques of speech training.

Subsequent chapters include children with voice disorders, children with hesitant speech, children of foreign tongues, and children with impaired hearing. Hesitant speech of children should be treated by experts and emphasis in this chapter is on prevention.

Chapters reflect the viewpoints of the authors but all are filled with practical help to those contacting children with speech problems in the home, in the community, and in the schools.

HELEN S. LANE, PH.D.

Love Is Not Enough. Bruno Bettelheim. Glencoe, Ill., 1950, The Free Press, 386 pages. Price $4.50.

This is a book which will probably become a classic in the tradition of such works as Aichhorn's "Wayward Youth." The author, a student of Aichhorn's, is an eminently qualified psychologist and educator with the capacity to communicate his experience in a well-organized and lucid manner.

The book deals with the problems of children who did not have the opportunity of developing the kind of object relationships that would enable them to function in a world of reality. As a last resort these children were placed in a "psychiatric school"—the Sonia Shankman Orthogenic School of the University of Chicago.

At this school "the major tools in helping the child are the impact of a planfully controlled environment and of personal relations." These tools are employed in a round-the-clock program through a teamwork approach that includes all of the staff. The progress is based on an understanding of the dynamics of the child's problems and of therapeutic relationships, both individual and group. It is geared to the needs and capacities of the individual child and has as its goal helping the child to acquire "that greatest art of all: how to live a socially useful and emotionally satisfying life."

Although these are seriously disturbed children their problems are just exaggerations of all problems of growth and development. Through the exaggerations it is possible to see more clearly how distortions occur and how they can be prevented and treated. This book should enhance the understanding of all who are concerned with the development and maturation of children.

WARSON.

Editor's Column

TUBERCULOUS MENINGITIS

TUBERCULOUS meningitis is a curable disease'' was the conclusion reached by ''experts'' from ten different countries at a meeting held in Paris in February, 1950, organized by UNICEF and WHO. The report of this conference on the ''Streptomycin Treatment of Acute Tuberculosis in Children'' has recently been made available by the International Children's Centre in Paris.*

Tuberculous meningitis is looked upon as neither a rare nor common disease in the United States, where the records of most large urban clinics will show from six to twelve admissions yearly. There were 383 deaths from this cause reported in the entire United States for the year 1948 for children under 4 years of age. However, it is an uncommon disease on this side of the Atlantic when contrasted with some of the figures referred to in the report for European clinics. Thus La Salpétrière Centre in Paris reported on the treatment of 250 cases, Prof. Dubois of Brussels referred to 173 cases treated in twenty-eight months, Prof. Cocchi of Florence to 223 in two years, and the Marseilles clinic to 163 in one year. This vast amount of material permits of controls, statistical studies, and experimental changes in the method, rhythm, and length of treatment; hence the European experience is of great importance to the clinic or hospital which admits but a few cases each year.

There was a general agreement on many points as regards streptomycin treatment and its results. The younger the child the higher the mortality. For example, Dr. Brissaud of Paris reported a mortality of 75 per cent for children less than a year old, 42 per cent for children 1 to 6 years of age (118 cases), 37 per cent for children 6 to 20 years of age (128 cases). A second most important factor is the length of time elapsing between the onset of the disease, its diagnosis, and the beginning of treatment.

The discussion centered on the method of treatment, and the conference reached certain general conclusions which were presented as recommendations as of Feb. 12, 1950, which may well serve as a guide for those who see only an occasional case. To quote:

''Streptomycin is the basic remedy. Its introduction into the meningeal spaces is indispensable in all cases.

''*The administration of streptomycin by the intramuscular route must be both continuous and prolonged.*

''*Continuous:* There should be no interruptions, not even short ones, at least during the first months of treatment.

''The number of daily injections has been reduced to two by some authors, apparently without detriment.

''*Dose:* The dosage adopted has varied from 20 to 50 mg./kg. per day according to the authors, with a daily maximum of 60 cg. to 1 g. Under these conditions younger infants receive a proportionately larger dosage than older children.

*Streptomycin Treatment of Acute Tuberculosis in Children, Paris, 1950, published for the UNICEF by the International Children's Centre. Collected Papers and Documents. I.

"*Prolonged:* The treatment should be continued beyond complete recovery.

"The majority of authors believe that this requirement is fulfilled 2 months after the C. S. fluid returns to normal.

"*Administration into the meningeal spaces is usually accomplished by intrathecal injection.*

"The dosage for intrathecal injections varies by author and case from 20 to 50 mg., according to the age and weight of the patient.

"*Rhythm:* The rhythm of injections is usually 1 per day. In some cases, 2 injections per day may be prescribed for the first 8 to 10 days or when evolutive recurrences occur. Daily injections should be continued for several weeks, after which the intrathecal injections may be spaced out to longer intervals, but the intrathecal route should not be abandoned until the C. S. fluid is normal.

"Since streptomycin should be applied to the focus itself, in cases of bad circulation of the C. S. fluid an upper route is recommended, i.e., suboccipital or ventricular, even after a surgical intervention. When an upper route is used, the dosage should be reduced by one-half.

"Association with other antibiotics is recommended.

"The control of children in whom an onset of tuberculous meningitis may be suspected (recent infection in very young infants, micronodulary tuberculosis, etc.), requires lumbar punctures, repeated if necessary, which are in such circumstances innocuous.

"After recovery, supervision of the C. S. fluid by lumbar punctures is absolutely indispensable in order to foretell recurrences or relapses. In general, continued observation of children considered as having recovered is necessary."

Among the associated antibiotics, the subject presented by Dr. Edith Lincoln of New York, promizole of the sulfones and para-amino-salicylic acid are chiefly in use.

One of the most interesting phases of the discussion was the role of the neurosurgeon presented by Dr. Honor Smith of Oxford, and Dr. J. Lepintre of Paris. In the European clinics, the neurosurgeons are taking an increasingly important part in the treatment of the disease. Surgery is used for two purposes. Dr. Smith uses bifrontal burrholes so that streptomycin can be injected through a needle into the ventricles, and thus circumvent mechanical blocking. Major operations are used to cleanse the lesions and adhesions, particularly those at the base of the brain. The site and technique vary from case to case as determined by the ventriculographic and anatomical findings. Dr. Lepintre considers progressive and rapid weakening of vision, and acute intracranial hypertension as indications for operation. In Dr. Lepintre's clinic ten out of forty-one children with operations survived. Success, he feels, depends in part on the time relation of the operation to the onset of the disease. Five of eleven patients survived when operated upon within the first month after onset as contrasted with one in seventeen operated upon after the third month following onset.

This particular international conference on a specific subject was obviously of far greater value than the usual international conference. The report itself is an excellent one and shows careful compilation and editing.